

**METHODS FOR THE SYNTHESSES OF COMPOSITIONALLY DIVERSE  
DENDRIMERS USING CHEMOSELECTIVE ROUTES**

A Dissertation

by

MACKAY BAGLEY STEFFENSEN

Submitted to the Office of Graduate Studies of  
Texas A&M University  
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2004

Major Subject: Chemistry

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August 2004

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## ABSTRACT

Methods for the Syntheses of Compositionally Diverse Dendrimers  
Using Chemoselective Routes.

(August 2004)

Mackay Bagley Steffensen, B.S., Southern Utah University  
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Dendrimers are a unique class of macromolecules that present perfect branching on a molecular scale. The pattern of branching at the atomic scale is compared to the branching of trees, from whence dendrimers get their name. Dendrimers have been attractive synthetic targets for the past twenty years. The methods and building blocks used in the synthesis of dendrimers vary, but molecules of this class of polymeric materials all possess symmetrical branching emanating from the core. At each branch point the number of groups increases exponentially. Efforts directed toward the synthesis of dendrimers presenting multiple functional groups at the surface and within the dendrimer structure are described.

Methods are described which provide access to dendrimers in a one-pot per generation fashion, with triazines as the common moiety. Chemoselective routes utilize the temperature dependant substitution of cyanuric chloride to construct dendrimers, obviating the use of protected monomers or the need to manipulate functional groups during the synthesis. These methods are atom economical, as the only by-products are HCl and a base to scavenge it. The methods are efficient, with typical isolated yields of product in the middle to high ninety percent range, often on a multi-gram scale. Methods are described for conducting three separate reactions in a single pot. Specific emphasis is placed on structural control of the interior and surface groups of the dendrimers.

The synthesis of a G3 dendrimer of layered composition is described. The use of a different difunctional linkage group for each generation of dendrimer growth produced a G3 dendrimer with layered composition without the use of protecting groups or functional group interconversions.

A G3 dendrimer was synthesized presenting five different functionalities at the periphery on a 10 gram scale, resulting in approximately 70% overall yield. The peripheral

groups are composed of orthogonal functionality, which can be independently and selectively unmasked or manipulated in the presence of the other functionality.

The syntheses of dendrimers incorporating the short linker hydrazine produce materials with interesting physical properties as well as a low ratio of carbon to nitrogen. The use of dendrimers in the construction of novel macromolecular constructs is also described.

**To:**  
**Mariam, McKade, MaKella, Madalyn, and Malayna:**  
**My Little M-Empire.**

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I am indebted to Dr. Eric Simanek for allowing me the freedom to work in his group and explore my own ideas and most importantly to do what I love, mix chemicals.

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## CHAPTER I

### INTRODUCTION

#### 1.1 From Polymers to Dendrimers

The history and development of organic chemistry is inextricably woven with the development of total synthesis. Wöhler's synthesis of urea opened the era of organic synthesis with the realization that construction of natural molecules could be carried out in a laboratory.<sup>1</sup> Organic chemistry developed quickly thereafter as it was realized chemists could accomplish what was considered only nature's domain. Methods for the structural elucidation of natural molecules by deconstructing them to smaller known compounds were rapidly followed by routes and synthetic tools to mimic nature and construct natural products. To control the connectivity and placement of atoms in the construction of a molecule, especially if nature has already conquered its synthesis, is one of the appeals of organic chemistry.<sup>2</sup> Nature produces a plethora of unique carbon skeletal arrangements which organic chemists pursue in their quest to mimic nature. The variety of functional groups found appended to and imbedded within the carbon skeletons, with specific topological arrangement, attests to the fecundity of nature as an organic chemist. The original driving force of total synthesis to construct a synthetic molecule to confirm the structure of a natural product<sup>3</sup> is slowly being supplanted by more utilitarian endeavors such as the development of therapeutically relevant molecules. Perhaps the greater contribution made, and which remains to be made, from total synthesis is the development of a well-defined discipline with an ever increasing collection of methods and tools for the construction of complex molecular structures.<sup>4</sup>

Polymers are ubiquitous natural products, fulfilling both structural and functional roles. The development of polymer chemistry as a discipline evolved in an asynchronous manner compared to organic chemistry. As more was learned about the structure of natural products greater feats were accomplished through efforts to synthesize them. Discoveries achieved in understanding natural polymers did not necessarily translate into a more in-depth understanding of synthetic polymer chemistry, and vice versa. The first macromolecules investigated in detail were the natural polymers rubber, cotton (cellulose), silk and wood resins, but the chemical

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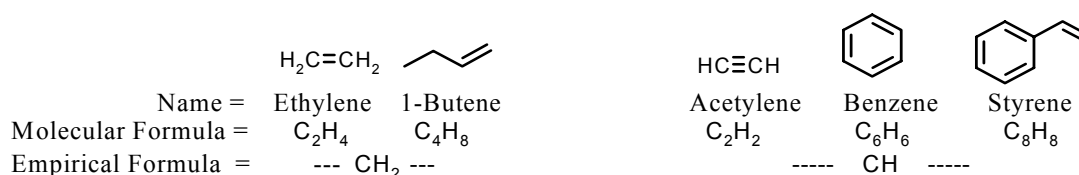
This dissertation follows the style and format of the journal *Tetrahedron*.

structures of these materials were unknown before the first decades of the 20<sup>th</sup> century, and thus the pursuit of their syntheses before this period would have been absurd.

The initial foundation laid for polymer chemistry was framed from industrial pursuits to convert the natural polymers into manageable and functional materials.<sup>5</sup> Perhaps the complexity of natural polymers inhibited their use as the founding molecules for understanding the basic principles of polymer chemistry. It was the investigation of simpler synthetic macromolecules which provided the fundamental theories and intuition necessary for the development of polymer chemistry as a science.

## 1.2 Difficulties in the Emergence of Polymer Chemistry as a Science

The initial derivation of the polymer concept began in 1826 with the discovery of butene by Faraday. Butene was found to have a gas density twice that of the known molecule ethylene, but they both have the same elemental composition. At the time it was thought the elemental composition of a material defined the properties of a chemical compound, but here were two compounds with the identical elemental composition, but markedly different properties. Berzelius suggested in 1827 and later refined in 1833 a concept similar to isomers. A compound having the identical elemental composition as a reference compound, but possessing different physical properties, was termed a polymer of the reference molecule. Butene is thus referred to as a polymer of ethylene, and even in some cases benzene and styrene assigned as polymers of acetylene (Figure 1.1). It would take over a century before a concise definition and basic understanding was established of what truly constitutes a polymer. The lack of a clear understanding concerning the connectivity of atoms until the late 1800's hampered the scientific community's ability to comprehend the essence of large polymeric molecules, nevertheless contemplate the construction of such molecules.



**Figure 1.1.** Polymers according to the original definition of Berzelius. Butene, with the empirical formula of  $\text{CH}_2$  was considered a polymer of ethylene. Benzene and styrene with an empirical formula of  $\text{CH}$  were sometimes described as polymers of acetylene.

### *1.2.1 Setbacks*

Early progress was achieved in the production of polymeric materials and more importantly the ability to modify natural polymers, imparting new properties and uses for the natural products. These industrial advances in polymer chemistry were accomplished at the turn of the 20<sup>th</sup> century in the absence of any sound theoretical basis.<sup>6</sup> Kekulé began to advocate his theories concerning the connectivity of atoms just as the inimical colloidal theory devised by Thomas Graham in 1861 began to take hold. For three-score years the colloidal postulate would poison the thought and hinder the development of an accurate theory to deal with polymers. Graham's work distinguished between colloids (aggregates of small molecules held together by some undefined secondary valence force) and crystalloids (small organic molecules) on the basis of the ability of a solution of the molecule in question to pass through a membrane. While Graham's theory possesses some scientific merit, the persistent application of the colloidal theory in explanation of properties observed for macromolecular materials hindered the development of polymer chemistry.<sup>7</sup> It was not uncommon at the turn of the 20<sup>th</sup> century for scientists to attribute phenomenon now understood to result from the structure and properties of polymeric molecules to an ill defined colloidal state.

Under the tutelage of Kekulé the theoretical groundwork was laid for organic chemists to define the atomic connectivity of natural products. It was realized by the late 1800's that atomic connectivity, and not only elemental composition, defines many of the observable physical properties of a molecule. A second trend emerged in collusion with the colloidal theory which retarded the investigation into molecules of high molecular weight; the inclination to define real chemistry during this period by the standard of "the molecule and its representation by a concise graphical (or structural) representation (as) the prime object of all effort."<sup>8</sup> An early stimulus for organic chemists was the identification of a pure substance, ascribing to it a definite atomic composition with a single molecular formula and the establishment of a single atomic structure. Flory described it best with "The investigator was obliged to adduce elementary analyses to confirm the composition, and to supplement these with molecular weight determinations for the purpose of showing the substance was neither more nor less complex than the formula proposed. Otherwise the fruits of his labors would not be elevated to an honored place in the immortal pages of the chemical compendiums."<sup>9</sup>

With the conceptual framework and theory of atomic connectivity in hand, the erection of organic chemistry as an indomitable fortress and haven for fruitful discovery was well under

construction. The compilation of techniques to deduce the structures of nature derived products accelerated efforts and the identification of tools and reactions for their total synthesis. Polymers were relegated to a lower caste, considered assemblies of small molecules, held in a ‘colloidal state’ by ‘secondary valence’ forces. How could a structural representation be assigned to such an ephemeral and evanescent ‘colloidal state’? While experiment upheld theory regarding atomic connectivity, the ‘secondary valence’ forces responsible for holding matter in the colloidal state had no such experimental support.

Chemists are not entirely to blame for their slow discovery of polymers, as macromolecules are generally obtained as mixtures of molecules with a distribution of chain lengths and thus different molecular weights. Polymers did not yield to the rudimentary techniques used to characterize organic molecules during this period. A single concise molecular formula can not be determined for a mixture of molecules. In addition polymers should have end-groups, but the identification of which overtaxed the analytical methods of the time.<sup>8</sup> The inability to define a precise molecular formula and identify the nature of the ends groups, in conjunction with elemental analyses which provided data corresponding to the monomer or similar small molecule left the structures of polymers undefined. Clever assumptions were made to account for the data which could be gleaned from the stubborn molecules, such as the common resolution concerning the identity of the end groups; the molecules were considered cyclic, and thus did not have end groups. Others were clever enough to suggest that end groups might be present, but the molecules may be so large that their effective concentration would extend beyond the limits of detection. Lourenço conceived this idea as early as 1860; however the common trend remained for half a century more to accept the idea of polymers as composed of small cyclic molecules held together by secondary valence interactions.

### *1.2.2 Advances*

Small battles were won advancing chemists closer to the fortress encompassing the enigmatic polymer during the late 1800’s. While the correct definition of polymers was slow to emerge, understanding their nature and properties was achieved early. Berthelot was able to isolate the dimer, trimer, and tetramer of pentene, and presented the results in a lecture titled ‘la polymérie’ to the Chemical Society of Paris in 1863. His discoveries were insightful, but the theory of atomic bonding was still in the developmental stage. After expounding his

experimental results Berthelot waxed more philosophical speculating the principles of polymerization may also apply to atoms, where sulfur may be viewed as a dimer, and tellurium a tetramer of oxygen. Lourenço, who correctly offered a solution to the missing end groups of polymers, conducted a series of reactions between 1859 and 1863 on the polycondensation of ethylene glycol. A series of oligomers containing up to six units (hexaethylene glycol) were isolated through distillation of the reaction. Lourenço hypothesized the residue which remained could contain molecules with up to *one hundred* glycol units. Lourenço's work inspired the suggestion that the molecules remaining may be so large that the end groups are insignificant contributors to the composition and reactivity of the molecules as a whole.

### *1.2.3 The role of natural polymers in the development of polymer science*

Natural polymers played an important part in the early stages of dendrimer evolution. Rubber was one of the first natural polymers to receive detailed investigation with the empirical formula deduced by Faraday in 1826. Williams burned rubber in 1860 screeching to the realization that isoprene could be isolated from the destructive distillation of rubber. Raoult's freezing-point depression method, devised only a few years previous, was used by Gladstone and Hibbert in 1888-1889 to ascribe rubber a molecular weight of 6,000-12,000 "if the method holds good."<sup>10</sup> It was the efforts of Harries, initiated in 1904, which began to define the atomic structure of rubber. Concern over the nature of the end groups almost caused Harries to erase the progress made to that point through his first proposal of rubber as a cyclic dimer of isoprene (dimethylcyclooctadiene, Figure 1.2). In subsequent years the number was inflated to larger rings, composed of five, seven, and eventually nine isoprene molecules. These small rings were thought to be held together by secondary valence forces, mostly attributed to the presence of the double-bonds.



**Figure 1.2.** The structures of isoprene and dimethylcyclooctadiene.



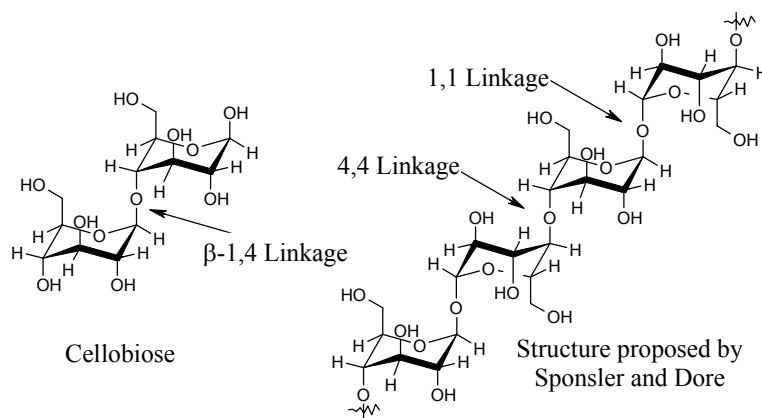
Pickles did not accept the cyclic dimer idea, as the small molecule could not be distilled from the assumed aggregate. In 1910 Pickles provided an intellectual dilemma, showing the bromination of rubber, with the concomitant removal of the double-bonds, did not affect the colloidal nature of rubber.<sup>11</sup> Pickles suggested the true rubber molecule was much larger, but still accepted the idea that the ends were joined to form a ring, like the bands around a barrel. In 1922 Staudinger demonstrated reduction of the double-bonds in rubber by hydrogenation did not change the properties attributed to the ‘colloidal state.’ A light came on and Staudinger suggested the double-bonds played no role in defining the macromolecular structure of rubber. He bounced around the idea that rubber molecules were held together by primary valence bonds, and thus their structure could be explained by atomic connectivity theories employed at that time by traditional organic chemists. The fortress of the polymer had been breached and the light shed by Staudinger soon illuminated the true nature of macromolecules, with organic chemists finding refuge and sustenance within her walls.

The idea that carbohydrates are polymeric materials dates back at least to 1871 when Hlasiwetz and Habermann suggested these compounds are mixtures of several isomeric and polymeric substances, differing from one another by the degree of molecular condensation. In 1889 Brown and Morris used Raoult’s method to obtain a molecular weight of 30,000 for amyloextrin.<sup>12</sup> Such a large molecular weight, suggesting a very large molecule, was met with more than just skepticism leading to a decay in the confidence of Raoult’s method and later colligative properties in general for the analysis of colloidal solutions. In 1921 the influential chemist Karrer laughed at the idea that nature would construct such large molecules as starch for the storage of sugar since “it is improbable that a plant in converting sugar to a reserve substance from which it might soon have to be recovered would perform such complex work.” It was known that glucose could be obtained almost quantitatively by the degradation of cellulose as early as 1913, but the structure of cellulose was assumed to be a ring built up from glucose units. The common opinion held at the time concerning the structure of cellulose as expressed by Heuser in 1922 was “according to the most recent investigations the principle of the chain formula must be abandoned.”<sup>13</sup>

#### *1.2.4 The role of analytical methods in advancing polymer chemistry as a science*

Early X-ray diffraction studies indicated the unit cells of cellulose, silk and crystalline rubber were similar in size to those of known small molecules. The unit cell was argued as a

confining feature of the compound and it was thought that natural polymers could be no larger than the molecules contained in the unit cell as determined through X-ray analysis. Polymers were about to be relegated to an intellectual dungeon as the X-ray data was used as further support for the notion that rubber, cellulose, and silk were composed of small molecules. Sponsler and Dore provided X-ray diffraction data consistent with cellulose fibers composed of an indefinite number of units in 1926. However, they also proposed a structure inconsistent with the chemical evidence present at the time concerning the constitution of cellulose. From the X-ray data they proposed a molecule composed of glucose units linked by alternating 1,1 and 4,4 linkages (Figure 1.3). Chemists had conclusively demonstrated that cellulose was composed of cellobiose, a disaccharide linked through a  $\beta$ -1,4 connection (Figure 1.3). The incorrect assignment proposed in by Sponsler and Dore in their paper only further shed doubt of the validity of any claims made about the macromolecular structure of cellulose, and the applicability of X-rays in studying organic molecules in general.



**Figure 1.3.** The structure of cellobiose and the proposed structure of cellulose according to Sponsler and Dore. Cellobiose is a disaccharide composed of glucose units joined by a  $\beta$ -1,4 linkage. Cellulose is a polymer of glucose monomers joined by  $\beta$ -1,4 linkages. Sponsler and Dore proposed a structure for cellulose composed of alternating 1,1 and 4,4 glucose linkages in 1926.

Peptides and proteins were better understood than some of their simpler siblings, and this was facilitated by the ability to isolate homogenous, mono-disperse, and even crystalline protein samples. In many ways protein chemists were a step ahead of their organic chemist

counterparts in understanding the macromolecular nature of proteins.<sup>14</sup> Sulfur found in proteins from the amino acids cysteine and methionine provided an analytical handle for the determination of a protein's large molecular weight. Since most proteins contain at least a single sulfur-containing residue, and generally not too many more, the elemental analysis of pure proteins produces a low percentage of sulfur in relation to the carbon, nitrogen, oxygen, and hydrogen content. The small percentage of sulfur translates into a large ratio of carbon to sulfur and a corresponding high molecular weight. The elemental determination of other natural polymers composed entirely of carbon, hydrogen, and/or nitrogen and oxygen provides an empirical formula with approximately equal atomic abundance. The result is a molecular formula more representative of the monomer than the polymer. Using elemental analysis, including the determination of sulfur, twenty-four proteins were found in 1902 to have an average molecular weight of 15,000.<sup>15</sup> The low abundance of iron in hemoglobin and the ability to obtain crystalline samples led to the reproducible determination of 0.4% iron in the hemoglobin sample. Assuming one iron per monomer a minimal molecular weight of 16,700 was proposed as early as 1886.

The use of X-rays was not the only analytical tool to expose the true nature of proteins. The development of the ultracentrifuge by Svedberg began to turn the tide in favor of a correct understanding of polymers. Svedberg initially settled on conducting sedimentation experiments of true colloidal solutions. The technique was valuable in determining accurate molecular weights of colloidal samples over a range from thousands to millions, but the value of the centrifuge did not stop there. Information on the distribution of particle weights could also be obtained. Svedberg, in turning his technique to the study of proteins, fully expected to see a disperse collection of molecules, but found exactly the opposite. The ultracentrifuge provided an analytical tool for the demonstrating the discrete monomolecular nature of proteins; they behaved nothing like known inorganic colloidal solutions. Svedberg's ultracentrifuge and sedimentation experiments settled the debate concerning hemoglobin; it turned out to be composed of discrete particles of large molecular mass. The results cemented the foundation for the acceptance of proteins as large molecules composed of a single molecular entity, and not assemblies of smaller polypeptides. The analytical ultracentrifuge, also pioneered by Svedberg, is used in the accurate determination of molecular weights of large molecules. The development of sensitive analytical methods to dissect the nature and properties of natural polymers provided conclusive evidence for their existence as large molecules. Beginning with Raoult's method of

freezing point depression it was the development of analytical techniques which slowly decreased the animosity towards polymer chemists and turned the field in to a fruitful discipline.

#### *1.2.5 Confusion abounds concerning the nature of proteins*

It has been suggested that many protein chemists did not capitulate to the convoluted colloidal theory,<sup>16</sup> but several noted chemists at the turn of the century still questioned the relationship between large molecules and proteins. The polypeptide theory proposed in 1902 correctly identified the principles involved in the bonding of amino acids to form peptides, but the relation of peptides to proteins and proteins to enzymes was still unclear. Emil Fischer approached the structural elucidation of proteins by a classical organic approach, through their synthesis. Fischer expressed doubts concerning the existence of proteins with molecular weights exceeding four thousand during a lecture as late as 1913.<sup>17</sup> During this same lecture Fischer described the synthesis of a molecule with a mass of 4,021, claiming it was the largest substance to date produced wholly by synthesis. He challenged the molecular physicists then studying high molecular weight substances to: “confine themselves to the synthetic products of known composition.” Fischer called upon organic chemists to “accumulate larger and larger masses in the molecules, in order to see how far... matter can go.” Fischer’s desire to pursue the construction of large molecules was evident, but the tools necessary for the synthesis of truly high molecular weight compounds of known composition was decades away.

Some protein chemists during Fischer’s time had ‘seen the light’, thus avoiding the pitfalls encountered through adoption and application the colloidal theory. One such investigator was Sørensen, the developer of the pH scale, who measured the molecular weight of crystalline egg albumin by osmotic pressure, and concluded that many of the beliefs long held by colloidal chemists were inaccurate. Sørensen issued a stinging condemnation of colloidal chemistry in 1915, stating “colloidal chemistry has, in my opinion, not contributed to further progress, but rather the reverse.”

### **1.3 Evolution of the Macromolecular Hypothesis**

It was the persistence of Hermann Staudinger and the development of synthetic polymers which finally provided the push necessary to establish a correct definition and conceptual framework for discussing polymers intelligently. Staudinger proved the force

necessary to establish a correct theory of polymers and macromolecules as large assemblies of covalently connected atoms.<sup>18</sup>

### *1.3.1 The doctrine of polymers: Hermann Staudinger*

At the beginning of the 1920's much was already known concerning polymers; polymeric materials were in household use. Cellophane, rayon, and Bakelite plastic dinnerware were common polymeric materials. Colloidal chemists possessed the louder voice during this period and were the accepted school of thought among chemists at the time. Hermann Staudinger left his research in organic chemistry, for which he had already established a sound reputation and developed a reaction which still bears his name,<sup>19</sup> to fight for the acceptance of macromolecules as covalent assemblies. His approach was to use simpler synthetic polymers as models of the natural counterparts, thus polyoxymethylene was used as a model for carbohydrates, polystyrene as a model for rubber, and polyacrylic acid as an analog of proteins.

Staudinger adhered to the initial definition of polymers proposed by Berzelius; a polymer has the same elemental composition as the monomer. Staudinger reserved the term 'polymer' to addition polymers such as rubber, excluding the condensation polymers of proteins, oligosaccharides, and DNA. Macromolecule was a term introduced by Staudinger which was free from ambiguities associated with the inconsistent application of the term polymer. Macromolecule was more inclusive than Berzelius' original term, including addition and condensation polymers. His macromolecular hypothesis first proposed in 1920 was met with resistance. He later refined his thoughts using his work on the hydrogenation of rubber with the definition of macromolecules as primary-valence chain systems. A defining statement expressing the chemical community's thoughts with regards to macromolecular chemistry during this period was made after a farewell lecture given by Staudinger in 1925 at the ETH in Zürich. A noted chemist compared Staudinger's championship of large molecules to that of a traveler in Africa claiming to have seen a zebra 400 meters long.<sup>20</sup> Such was the inability of organic chemists to accept the idea of large molecules at this time.

The identity of the end groups was a persistent thorn in framing the conceptual ideas of what constitutes a polymer. Staudinger was the first to effectively champion the existence of large molecules, but he still perpetuated some errors. To deal with the identity of the end groups Staudinger first suggested they may be composed of unfilled valences. These radicals were suggested to be stable on the basis of spatial separation of the reactive groups by the length of

the polymer. Staudinger later regressed, suggesting in 1929 that rubber and polystyrene were likely to be composed of very large rings; the same fanciful conclusion continued to come around and around. Staudinger also viewed polymer chains as rigid rods, a theory later superseded by the chain entanglement model.

### *1.3.2 An organic chemist for polymers: Wallace Carothers*

It was perhaps the work of Wallace Carothers while at Du Pont that finally convinced chemists that macromolecules existed, and clarified the dilemma associated with trying to identify the end groups of polymers. He set out specifically in 1929 to set aside some of the common misconceptions and to prepare polymers of definite structure through the use of established organic reactions.<sup>21</sup> Carothers' treatise in *Chemical Reviews* in 1931<sup>22</sup> defines many of the concepts and the current definition of polymers in use today; it is viewed as a turning point in the chemistry community's acceptance of polymer chemistry. Carothers efforts are comparable to the methodical approach utilized by Emil Fischer, "discarding, however, the unnecessary and severely encumbering insistence on pure chemical individuals under which Fischer and his colleagues labored."<sup>23</sup>

### *1.3.3 The academic community begins to accept polymers*

Polymer chemistry had arrived as a scientific discipline, but not to the open arms of the organic chemistry community. The general opinion of macromolecules at the time was summarized by Willstaetter in 1926 after a conference which was organized to confront Staudinger.<sup>24</sup> He commented that "such enormous organic molecules are not to my personal liking but it appears that we all shall have to become acquainted with them." By the "beginning of the 1930's the existence of macromolecules was inescapable."<sup>18</sup> Over the next twenty years research on polymers would make invaluable contributions to science and humanity through the creation of new materials and the establishment of a new discipline in the field of chemistry.

## **1.4 The Rapid Evolution of Polymer Chemistry as a Science**

### *1.4.1 The movement of polymers from industry to academia*

The Second World War spurred the industrial development of polymer science as the demand for novel technologies and materials arose. The desire and need for a synthetic rubber and the United States backing of polymer research accelerated industrial efforts. The goals of

polymer chemists became more utilitarian as functional materials were needed in short order. Research during this period focused on the ability to produce functional materials by controlling the composition of a polymer with subsequent control over the properties of the material. Details concerning the atomic structures of polymers were less important, and the materials synthesized typically relied on the use of established reactions. Polymer chemists would experiment with reactants and catalysts until a polymerization would occur, followed by analysis of the products to determine what had occurred. The ability to create new materials and tune the properties of the polymers for a specific application became as much of an art as that found in the synthesis of natural products.

The end of the Second World War allowed polymers to receive the academic attention they needed. In 1946 the first polymer institute in the United States was established at the Brooklyn Polytechnic Institute, heralding the sustained investigation of polymer structures, properties, and composition.<sup>25</sup> The institute's founder, Hermann Mark, saw a need for journals in which to disseminate the rapidly generated experimental details. Mark was the initial editor of the *Journal of Polymer Science*, the first American chemistry journal dedicated to the publishing of research on macromolecules.

#### *1.4.2 Consensus on the structure of natural polymers*

A general consensus on the structures of the natural polymers was beginning to be reached by the end of the Second World War. Cellulose was proven to be composed of glucose units connected by  $\beta$ -1,4 linkages in 1928, showing no contradiction between chemical and X-ray data. It was conclusively demonstrated during the same year that rubber was constructed of isoprene units connected in a head-to-tail fashion containing all cis double-bonds. Silk and other proteins were known to be composed of amino acids connected by planar amide linkages. But the structure of DNA remained enigmatic, but not from lack of trying.

DNA was suggested to be composed of tetranucleotide units on the basis of a hypothesis first put forward by Levene in 1919.<sup>26</sup> Levene and Schmidt published in 1938 results describing preparations of DNA with molecular weights between 200,000 and 1 million. Upon storage or treatment with certain proteinaceous material smaller fragments would appear and this was suggested to occur by the depolymerization of DNA through the "dissociation of the tetranucleotides of high molecular weight to those of lower molecular weight."<sup>27</sup> It was the studies of Singer, Caspersson, and Hammarsten which straightened out the dilemma,

demonstrating the rod like nature of DNA.<sup>28</sup> Chargraff set down the law with his rules describing the selective base pairing of the pyrimidine bases with the purine bases.<sup>29</sup> It wasn't until 1952 that the correct atomic connectivity of the nucleotides within DNA was deduced.<sup>30</sup> The tetranucleotide hypothesis, proposed for over three decades, was overturned in the early 1950 to reveal the correct identification of DNA as a polymer.

#### *1.4.3 The year of the polymer*

Polymer chemistry was an irrefutable science and had assumed its place along side total synthesis by the 1950's. The year 1953 could be termed the year of the polymer. In a scant quarter of a century polymer chemistry had moved from an ill-defined endeavor, lacking correct knowledge of concepts and a concise definition concerning the macromolecule realm, to a full fledged science with ample theories and techniques with which to probe the new domain. The publication of the 'polymer bible' by Flory titled *Principles in Polymer Chemistry*<sup>31</sup> in 1953 illustrated just how far the field had progressed. Polymer chemists had the tools necessary to describe polymer reactions and the products, and more importantly the theoretical methods and models necessary to deal with macromolecules. In April of 1953 the atomic structure of DNA as deduced by Watson and Crick was published.<sup>32</sup> DNA was a polymer composed of two antiparallel stands adopting a helical structure. Nature again had constructed a novel architecture, but this time on a macromolecular level. The claim to and inspiration born of unique molecular architecture was no longer just the domain of chemists studying and synthesizing natural products.

The Nobel Prize was awarded to Staudinger in the autumn of 1953, recognizing his contribution in understanding the nature and structure of macromolecules. His efforts had paid off, a new disciple had been established, and his work recognized. Carothers in all probability would have shared the stage with Staudinger for his methodical approach to the investigation of polymers, but his suicide at the age of 41 in 1937 not only cut too short a brilliant career,<sup>33</sup> but precluded his receiving this distinction.

In this same year that Staudinger received chemical history immortality the low pressure and temperature polymerization of ethylene was accomplished using Ziegler-Natta catalysts.<sup>34</sup> The value of this discovery is not only found in the profits gained through its industrial application, but the realization that controlling the properties of polymers can be accomplished through control of its composition, specifically in this case by the degree of polymer branching.



This discovery led to methods and catalysts providing control over the stereoarrangement of atoms within a polymer.

#### *1.4.4 Controlling the polymer*

Total synthesis reached new heights during the 1950's, and this is no better exemplified then with Woodward's synthesis of strychnine in 1954.<sup>35</sup> This alkaloid was described in 1952 by Sir Robert Robinson as "for its molecular size ... the most complex substance known,"<sup>36</sup> and while his familiarity with the molecule might prejudice his view, Woodward describes the case as a good one with strychnine containing "six nuclear asymmetric centers and seven rings constituted from only twenty-four skeletal atoms."<sup>35b</sup> What makes the synthesis so remarkable and impressive is the demonstration of the synthetic chemist's ability to mimic nature in controlling the placement of atoms within such a unique structure. Similar advances were occurring simultaneously in polymer chemistry.

In 1940 it was realized through infrared (IR) spectroscopic studies that polyethylene produced under high pressure contained more methyl groups present in the sample then could be accounted for by the end groups of the polymer.<sup>37</sup> This was the first realization that branching from the polymer backbone was occurring during the high temperature and pressure production of polyethylene. To study the effects of branching on the physical properties of the polymer diazomethane was polymerized to produce polymethylene, a polymer structurally homologous to polyethylene, but without branching. Polymerization of diazomethane in the presence of varying amounts of diazoethane gives a polymer with a controlled number of methyl branches. The incorporation of an increasing number of branches into the polymethylene polymer decreased its density, leading to the conclusion that low density polyethylene has a relative high degree of branching.<sup>38</sup> Rubber like polymers were produced when 15 or more methyl branches were incorporated for each 100 carbon atoms. The incorporation of a branch from the polymer backbone introduces a stereocenter at that point and under the above reactions the configuration of these methyl side chains was random.

The polymerization of propylene produces a linear polymer with a methyl side chain on every other carbon, and thus a stereocenter on every other carbon of the backbone. During the years 1953-1954 five patent applications were filed for the production of a stereoregular polypropylene polymer.<sup>39</sup> The production of crystalline polypropylene as described in the patents was the result of forming a stereoregular arrangement of the methyl side chains during

the polymerization of propylene. The importance composition of the polymer played in determining the physical properties of the final material was becoming evident; branching decreases the density of a polymer, while stereoregular features increase the crystallinity. The value of controlling the architecture of the macromolecule was beginning to be realized and the consequences were astounding.

The first total synthesis of a natural polymer occurred in 1954 using the catalysts developed by Ziegler and Natta. This work was conducted at the B. F. Goodrich Company by Horne and coworkers.<sup>40</sup> They polymerized isoprene in a head-to-tail fashion, producing a macromolecule containing virtually all cis bonds, the natural configuration of Hevea rubber. A few years later the Firestone Tire and Rubber Company produced polyisoprenes of very high cis content (>90%) using lithium as the catalyst.<sup>41</sup> The total synthesis of the natural oligopeptide oxytocin also occurred in 1954,<sup>42</sup> but being a nonapeptide it cannot quite be considered a macromolecule.

Two main factors separate synthetic polymers from their natural counterparts. First, nature has developed methods to control the composition of polymers down to the atomic level. Through the use of natural catalytic macromolecules (enzymes) nature can construct, modify, and manipulate natural polymers with atomic precision. Second, nature produces polymers, specifically proteins and ribonucleic acids, with low dispersity and even identical chain lengths and composition. Stereoregular polymers were the synthetic chemists' first success at controlling the structure of macromolecules. Methods for conducting living polymerizations followed a few years later in 1956,<sup>43</sup> further allowing chemists control over the composition of polymers and the ability to produce macromolecules possessing a narrow distribution of chain lengths. Many different architectural types are accessible using living polymerization methods,<sup>44</sup> although these were not pursued until the 1980's.

#### *1.4.5 Polymer chemists' attempts at mimicking nature*

The first efforts to control the atomic connectivity of a polymer at the monomer level came by way of inspiration from, or in desire to mimic nature. As in the synthesis of natural products nature has devised methods to construct macromolecules of controlled composition and structure. Nature's most impressive feat in relation to polymers is the ability to construct discrete copolymers, such as proteins, DNA and RNA, where every molecule in the sample has the same atomic connectivity; such molecules are considered monomolecular.

Synthetic copolymers have been known since the late 1800's. Copolymers allow the incorporation of multiple functionalities within a polymer through the use of multiple monomers, but also result in an increased heterogeneity in the polymer sample. Copolymers not only contain molecules of different lengths, but also molecules of different compositions and atomic connectivity by virtue of random assembly of the different monomer. Under certain conditions it becomes possible that no two molecules are exactly alike within a copolymer sample.

It is requisite that in the chemical synthesis of a peptide or protein, that the not only the composition of the molecule and the connectivity of the monomers be controlled at the atomic level, but also the stereochemical arrangement of the atoms. Little similarity between a biogenic peptide of choice and a peptide formed from the random polymerization of amino acids would be expected, and thus methods were devised to construct peptides in a step-wise manner.

The Nobel Prize winning Emil Fischer took the first steps to construct a truly monomolecular macromolecule. Fischer began work on proteins in 1901 with the synthesis of a dipeptide, and his efforts later culminated in the synthesis of an octadecapeptide of defined chemical composition in 1907. The molecular weight of Fischer's peptide was 1,212, not what polymer chemists would consider large today, but the feat in its time was monumental. Fischer's goal was to construct an enzyme. In a letter to Adolf Baeyer in 1905 he expressed this desire: "My entire yearning is directed towards the first synthetic enzyme. If its preparation falls into my lap with the synthesis of a natural protein material, I will consider my mission fulfilled."<sup>45</sup>

Fischer demonstrated that some physical properties of his synthetic peptides matched those of natural counterparts, in particular the synthetic peptides susceptibility to some proteolytic enzymes; however his peptides were composed only of leucines and glycines.

The first synthesis of a natural oligopeptide was accomplished in 1954 with the synthesis of the nonapeptide oxytocin by du Vigneaud,<sup>42</sup> for which he received the Nobel Prize in 1955. In 1956 he completed the synthesis of vasopressin, also a nonapeptide.<sup>46</sup> These peptides are considered small in relation to what nature can accomplish, containing ten less residues than the nonadecapeptide peptide constructed by one of Fisher's students in 1919. These efforts however paved the way for the successful synthesis of true macromolecular peptides. Total synthesis of proteins became more of a reality with advances in peptide synthesis made by Merrifield. Most notably he pioneered the solid supported synthesis of peptides by attaching them to an insoluble polymeric support, the union of synthetic polymers for the construction of natural polymers of

defined length, composition, stereoconfiguration, and atom connectivity. Through iterative reactions first involving the attachment of a protected monomer to the growing polymer chain, followed by removal of the protecting group located at the end of the polymer, and subsequent attachment of a new monomer, synthetic peptides and proteins can be constructed which are identical to those from natural sources. Merrifield received the Nobel Prize in 1984 for his efforts. His group synthesized multiple peptides, some of which could be considered macromolecular. The iterative nature of solid phase peptide synthesis quickly allowed the process to be automated.

True macromolecular proteins can be constructed by total synthesis routes.<sup>47</sup> Enzymes are typically composed of approximately 300 amino acid residues, with the smallest (e.g. ribonuclease, lysozyme) containing around 125 residues. The synthesis of sequences longer than one hundred residues is difficult by typical step-wise solid phase synthesis methodologies. The introduction of total chemical synthetic methods, which employ the use of ligation reactions to join smaller peptide fragments forming larger constructs, provides synthetic access for the production of large proteins.<sup>48</sup> The construction of novel enzymes containing all D-amino acids is a salient example of the current ability of chemists to control the composition, placement, and structure of macromolecules.<sup>49</sup>

Oligonucleotides succumbed to the same fate as proteins, that being the automated chemical synthesis of monomolecular biopolymers with the identical composition to those from a biogenic source down to the atomic connectivity and stereoarrangement. Marvin Caruthers spearheaded this endeavor, proving its value through the sequencing of the Human Genome, what has been termed from a chemist's perspective as the single largest undertaking for the structural elucidation of a natural product. The DNA double helix is a beautiful example of macromolecular architecture, and the ability to construct higher ordered novel molecular architectures using DNA has been accomplished by Seeman.<sup>50</sup> During the beginning of the 21<sup>st</sup> century reports began to surface regarding the automated synthesis of a third biopolymer: the oligosaccharides.<sup>51</sup>

The synthesis of linear biopolymers of known composition and atomic connectivity are now routinely conducted. Peptides can be synthesized in a few hours to days, and even the total chemical synthesis of enzymes is possible. Oligonucleotide synthesis is routine, greatly impacting research in the biosciences. Automated oligosaccharide synthesis provides rapid access to macromolecules greatly impacting the fields of glycobiology and glycomics.<sup>52</sup>

Polymer chemists have succeeded in conquering the syntheses of the natural polymeric products, so where do they turn to find the next target? Their imaginations.

### **1.5 Polymers Are Not Just Straight Chain Molecules**

Just as natural product chemists look for a new structure with unique architectural features to pursue, polymer chemist began to envision and seek unique macromolecules. The results of Ziegler and Natta introduced chemists to the idea of stereocontrol. Living polymerization offered opportunities for control over the size and molecular weight distribution of polymers. Developments and advances in directing copolymerizations offered access to compositional control. The stepwise synthesis of the natural macromolecules demonstrated control down to the atomic level in the construction of polymers. The ability and desire to control the architecture of macromolecules was last to develop.

Flory outlined multiple possible unique macromolecular architectures in his book in 1953. His treatment was theoretical in approach and dealt with the possibility of branching resulting from the use of multifunctional monomers in the polymerization process. Networked and cross-linked polymers were well known at the time, but most materials result from random branching and do not provide access to discrete macromolecules. One class of synthetic macromolecules has evolved to provide the construction of large assemblies of atoms in a controlled fashion, giving rise to discrete and monomolecular structures of known composition and atomic connectivity; these macromolecules are known as dendrimers.

#### *1.5.1 Polymer chemistry begins to branch out*

A high degree of branching is found in all levels of organization from the branching of trees (from whence the name dendrimers arises, from the Greek *dendri*-(branched tree-like) and *meros*-(part of), to the atomic level, where the efficiency of storage and access to sugars for metabolism is enhanced through the formation of highly branched oligosaccharides. The origins of dendrimer chemistry stretch back to the beginning of organic synthesis, and specifically the beginning of polymer chemistry, when it was realized that polymers could contain branching points, thus giving rise to branched structures. The covalently linked linear chain of branched and cross-linked polymers remains the characteristic feature of so-called non-linear polymers. In dendrimers branching becomes the dominant feature, and the synthesis of a dendrimer results in

the construction of a large monomolecular assembly of atoms presenting a perfect branching pattern.

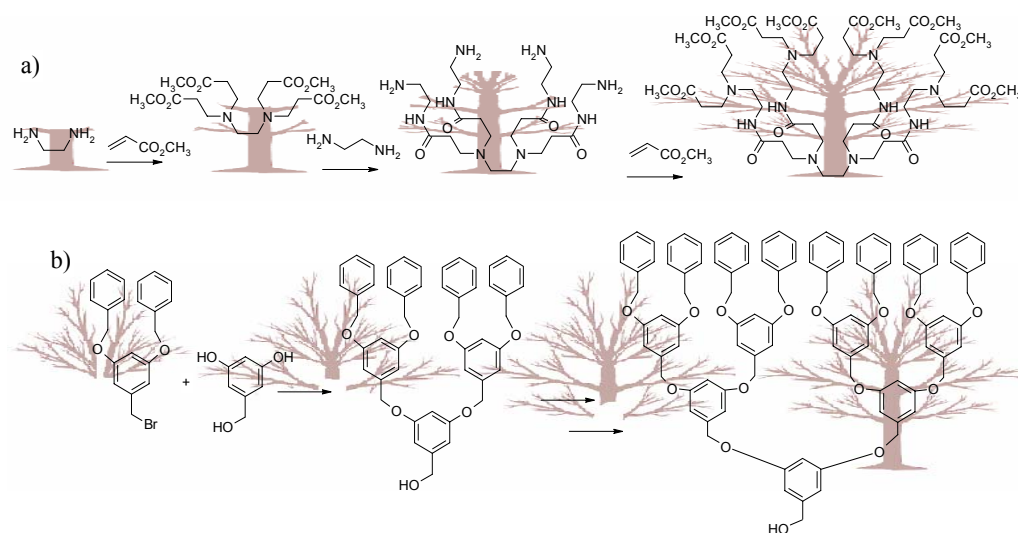
The field of dendrimer chemistry is a young research area, and represents a union between the traditional organic chemistry's ability and desire to control the connectivity and placement of atoms, with the subsequent production of a monomolecular structure, and the polymer chemist's ability to construct large assemblies of atoms with unique structural and physical properties.<sup>53</sup> Fischer would be proud, not only can molecules of extremely large mass be constructed, but a concise structural representation with atomic detail can be drawn for the dendrimer structure.

### *1.5.2 Dendrimer chemistry begins*

The first generally accepted synthesis of a dendrimer occurred in 1978 by Vögtle.<sup>54</sup> The products were termed cascade molecules, and occurred by the iterative application of two sets of reaction conditions. While these molecules were not specifically pursued for their highly branched structures, and were relatively small in nature, the synthetic methodology for the future construction of dendrimers had been outlined.

The only report until 1985 on the utility of Vögtle's 'cascade synthesis' methodology came in the form of three patents filed in 1979, 1981, and 1983 on the synthesis of lysine dendrimers.<sup>55</sup> These patents describe the synthesis of polylysine dendrimers using the  $\alpha$  and  $\epsilon$  amino groups as the branching points for the structure. The physical properties of the lysine dendrimers were characterized and the results published in a 1982 research paper.<sup>56</sup> In 1985 dendrimers received their name and the investigation began in earnest with the publication of two research papers. Newkome and coworkers published the synthesis of a series of molecules termed arborols (*arbor*-Latin for tree), possessing three branching points at each generation.<sup>57</sup> Tomalia and coworkers reported the synthesis of a series of poly(amidoamine) (PAMAM) dendrimers while at Dow.<sup>58</sup> The next advance in dendrimer chemistry, which supplied the methodology necessary to truly construct macromolecules with tailored structures, came with the publication of the convergent approach to the synthesis of dendrimers by Fréchet in 1990. Previous to this method dendrimers were constructed through what is termed a divergent strategy.

The divergent synthesis of dendrimers is likened to the way nature constructs trees (Figure 1.4a). The initial construction of the structure begins at the trunk of the tree or core of



**Figure 1.4.** Divergent (a) and convergent (b) dendrimer synthetic routes. An increase in the number of branching units in the divergent route occurs through reaction at the peripheral layer of the dendrimer. The branching in the convergent route is doubled by reaction of two monomers with a core molecule.

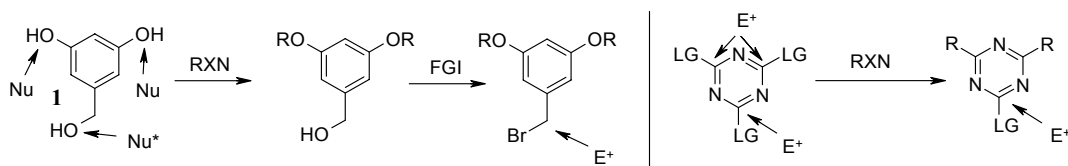
the dendrimer, and emanating from the core are appended a series of branches. On the end of these branches are appended more bifurcations, continuing outward to the surface of the tree or dendrimer. The branching at each level increases as a function of the number of branching points used. In Newkome's dendrimers the branching effectively tripled after the addition of each layer, while in Tomalia's initial example the branching doubled at each stage. The divergent method requires an exponential increase in the number of reactions at the dendrimer periphery which much be completed to ensure complete branching; incomplete reactions introduce defects and imperfect branching into the dendrimer structure.

The convergent method for the construction of dendrimers has been termed the organic chemist's approach to dendrimer synthesis (Figure 1.4b). The dendrimer is constructed from the branches toward the trunk utilizing a constant number of reactions for each generation of growth. The branching of the dendrimer is increased by connecting two (or more) branched molecules to a common core, effectively doubling (or more) the number of branches at the end of the molecule, but only necessitating two reactions. In the case of incomplete coupling reactions using the convergent route, the by-products have a fraction (approximately one-half) of the mass of the completed product, and are generally easy to separate from the desired product. Byproducts resulting from incomplete couplings using the divergent approach typically differ

from the desired product by only a small percentage of mass and thus are difficult, at the least, to separate from the desired product. The real power of the convergent route arises from the ability to control the composition of the dendrimer at each generation.

Fréchet's initial method used the bi-functional tri-substituted benzene **1**, which contains two phenolic groups and a benzylic alcohol (Figure 1.5). The phenolic oxygens are more acidic, and thus more nucleophilic than the benzylic alcohol under basic conditions, allowing selective modification at these two sites. Each phenol is of equal nucleophilicity and little selectivity of reaction between the two can be obtained. To accomplish modification of a single site on Fréchet's core a substoichiometric amount of the given reagent is used, followed by separation of the desired mono-derivatized product from the unmodified and bis-modified molecule. Functional group interconversion of the benzylic alcohol into a reactive electrophile is required after reaction of the phenol groups.

A unique approach to the construction of dendrimers is the use of a triazine core, where the branching necessary for dendrimer growth results from direct substitution onto the core, rather than through functional groups appended to the core. The nature of the functionality appended to the core can be altered by the selection of various nucleophiles. The triazine contains three electrophilic sites in contrast to Fréchet's monomer which has three nucleophiles of two different types (Figure 1.5). The electrophilic sites on the triazines can be reacted in a sequential temperature dependent manner. The first substitution introduces an electron donating group onto the ring, increasing the temperature or time required for subsequent reactions. The temperature dependent nucleophilic substitution of triazines has been known for decades, resulting in the construction of novel molecular architectures and application in a plethora of disciplines.

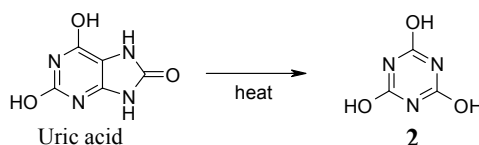


**Figure 1.5.** Fréchet's monomer contains three nucleophilic groups. The phenols being more nucleophilic react preferentially, followed by conversion of the benzylic alcohol into an electrophile. Nucleophilic substitutions on triazines occur sequentially in a temperature dependent manner, thus no functional group interconversion step is required.



### 1.6 The Discovery of Cyanuric Acid: The Start of Triazine Chemistry

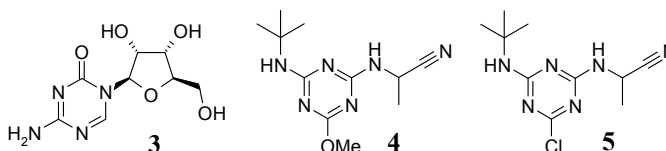
As a representative of the class of compounds known as 1,3,5, triazines or *s*-triazines (symmetrical), cyanuric acid (**2**) is one of the oldest recognized synthetic organic compounds. It was known as early as 1776 as ‘pyro-uric’ acid after its method of preparation by the pyrolysis of uric acid (Figure 1.6).<sup>59</sup> The name cyanuric acid is derived from the initial assessment that the molecule was composed of C≡N groups and was derived from uric acid. In 1820 cyanuric acid was again prepared from cyanogen in water by Serullas. It wasn’t until 1830 that Wöhler found that pyro-uric acid and Serullas’ product were identical. The first molecular formula was assigned through collaboration between Liebig and Wöhler as C<sub>6</sub>H<sub>6</sub>N<sub>6</sub>O<sub>6</sub>, but the correct formula, C<sub>3</sub>H<sub>3</sub>N<sub>3</sub>O<sub>3</sub>, was not determined until 1875. To further complicate matters a product isolated from the oxidation of uric acid was given the name tetracarbonimid, and was later found to be similar to cyanuric acid isolated from soil samples.<sup>60</sup> Soon researches confirmed the similarity of the two compounds and found that tetracarbonimid and cyanuric acid are the same.<sup>61</sup> It is interesting to note that while Wöhler is credited in 1828 with the first synthesis of an organic compound from an inorganic compound<sup>1</sup> an early but unrecognized natural product synthesis, that of cyanuric acid from inorganic precursors, occurred eight years earlier.



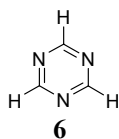
**Figure 1.6.** Destructive distillation of uric acid produces cyanuric acid, **2**.

Only a few reports of the triazine structure being found in natural products are present in the literature. The nucleotide analog aza cytidine (**3**) was isolated from fermentation broths in 1966, where the carbon at position C-5 of cytidine is replaced by nitrogen. Aza nucleotide analogs have found use as chemotherapeutic agents acting by inhibition of DNA synthesis.<sup>62</sup> The only additional reported natural occurrence of an *s*-triazine containing compound was a molecule isolated from an algae found off the coast of China; the product being named halimedin (**4**).<sup>63</sup> Halimedin differs from the widely used herbicide cyanazine (**5**) only by a methoxy substituent at the chloride position of cyanazine. The suggestion was later made that

isolation of halimedin was simply the recovery of a synthetic compound from a natural source.<sup>64</sup> The questions as to the source of the cyanazine in the South China Sea, or how the substitution of the chloride by the methoxy group occurred remain unanswered. Melamine (7, see below) was found in the Orgueil and Murchison meteorites, however it is not thought to arise from a natural source.<sup>65</sup>

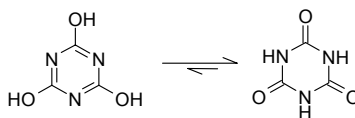


The parent compound of the triazine family, *s*-triazine (**6**) although originally synthesized in 1895 by Nef, eluded correct identification for nearly sixty years. Methods for the synthesis of *s*-triazine were pursued for many years, typically by the reduction of other *s*-triazine analogs. Grundmann and Kreutzberger convincingly demonstrated in 1954 the molecule prepared from the treatment of hydrogen cyanide with hydrogen chloride, long considered the dimer of hydrogen cyanide, was actually a trimer and the elusive *s*-triazine.<sup>66</sup> In comparison to cyanuric acid and other substituted triazines, *s*-triazine displays instability unique to this heterocyclic family. It is readily hydrolyzed in water, occurring immediately in the presence of dilute aqueous acids, producing ammonia and formic acid.



Cyanuric acid is found primarily in its oxo tautomer (Figure 1.7), and reactions with electrophiles tend to give *N*-substituted products. Cyanuric acid is of limited commercial importance, and of the 80,000 tons produced annually (1997) more than 90% is used to make *N*-

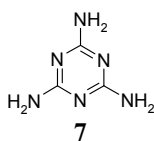
chlorinated isocyanurates. *N*-Chloroisocyanurates are used as swimming pool sanitizers, disinfectants, detergents, and industrial cleaners. Cyanuric acid finds limited use as a stabilizer for chlorine in swimming pools.<sup>67</sup> Other commercial products originating from cyanuric acid include tri-*N* substituted reagents for cross-linking polymers, light stabilizers, antioxidants, and flame retardants.



**Figure 1.7.** Tautomers of cyanuric acid. The equilibrium between the enol and oxo tautomers of cyanuric acid lies to the right, the oxo form.

#### 1.6.1 Melamine: The most widely used triazine

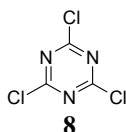
By far the most widely used triazine is that of cyanuric acids closely related structural cousin, melamine (**7**). In 2001 over 700,000 metric tons were produced, with a value of \$700 million. It is used as a crosslinking reagent in to formation of resins, most importantly those involving formaldehyde.



#### 1.6.2 Cyanuric chloride: A versatile molecule

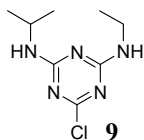
The annual production of cyanuric chloride (**8**) exceeds 100,000 tons annually. The synthetic utility and much of the industrial importance of the triazine heterocycle arises from the ease by which nucleophilic aromatic substitutions occur on halogenated triazines. The tri-fluoro, chloro, bromo, and iodo 1,3,5-triazines have been prepared, but 1,3,5-trichlorotriazine, cyanuric chloride, is by far the most important commercially and the most widely used synthetically.

Cyanuric chloride was first prepared in 1827, and its composition determined by Liebig in 1829. It is readily obtained through the cyclotrimerization of cyanogen chloride using activated charcoal as the catalyst.<sup>67</sup> More than 70% of the cyanuric chloride produced is used in the production of pesticides and especially the triazine herbicides. Nearly 70% of the cyanuric chloride produced annually is for the synthesis of the herbicide atrazine (**9**).



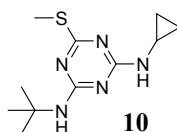
### 1.6.3 Triazine herbicides

The broadleaf herbicide atrazine (**9**) is one of the most widely used herbicides in the United States for weed control during the production of corn, sorghum, and other crops.<sup>68</sup> Although many European countries have banned its use, over 60 million pounds of atrazine are used annually in the United States.<sup>69</sup> As a result, atrazine is the most commonly detected herbicide in ground and standing water. Atrazine has been linked to health risks in animals and humankind.<sup>70</sup>



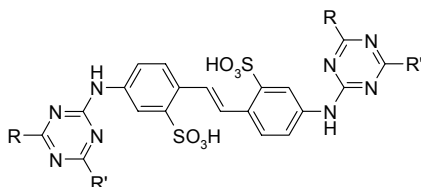
Prior to the late 1980's organotins were commonly used in antifouling paints on ships' hulls. Organotins such as tributyl tin (TbT) were found to be extremely toxic to marine organisms, particularly affecting the reproductive systems of shellfish. In the early 1990's, TbT was banned from application on boats under 25 meters in length. A full International Maritime Organization ban on the use of TbT on all ships went into force in 2003. The industry response

to the banning of TbT was the development of new antifouling paints formulated with copper and incorporating so called ‘booster biocides’ to prevent fouling. The triazine herbicide Irgarol 1051 (**10**) has become a common antifouling agent. Irgarol 1051 is designed to leach slowly from the paint to prevent buildup of biofilms on boat hulls. In 1993 Irgarol 1051 was found in coastal waters off of France at levels of 1.7 parts per billion.<sup>71</sup> Irgarol 1051 and other booster biocides are now detected in most coastal waters with shipping activity.<sup>72</sup> Irgarol 1051 is environmentally persistent with a reported half-life in seawater of between 100 and 200 days.<sup>73</sup>



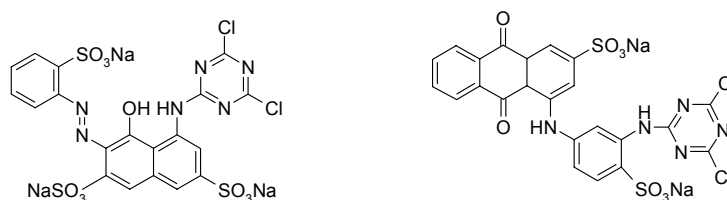
#### 1.6.4 Triazine optical brighteners and tie-dyes

Optical brighteners or fluorescent whitening agents are compounds added to materials such as textiles and papers to impart a more desirable appearance to the product.<sup>74</sup> The first optical brighteners appeared in 1941, and contained the triazine structure (Figure 1.8). They find use in everything from detergents and fabric treatments to coatings, inks, paints and plastics. In most cases they can be effective at concentrations ranging from 0.001 to 0.0001 of a percent by weight. The whitening effect is due to the absorbance of ultra violet light in the range from 300-430 nm and the emission of blue light between 400 and 500 nm. The net effect is the object appears ‘whiter’ under normal lighting conditions.



**Figure 1.8.** Typical structure of a triazine based optical brightener.

The triazine ring has found extensive use in the production of reactive dyes, which generally contain a monochlorotriazine, dichlorotriazine, or even a monofluorotriazine appended to a chromophore (Figure 1.9).<sup>75</sup> The dye is covalently bound to fabrics through a substitution reaction between the triazine and a hydroxyl or amine group present in the fabric. The triazine simply acts to anchor the dye to the fabric. The introduction of two dichlorotriazines, one on each end of the chromophore, shows a higher degree of fixation to the fiber, and is found as a component of many textile dyes. Triazine dyes can be purchased for home tie-dye use.



**Figure 1.9.** Typical reactive triazine dyes. Brilliant red and brilliant yellow.

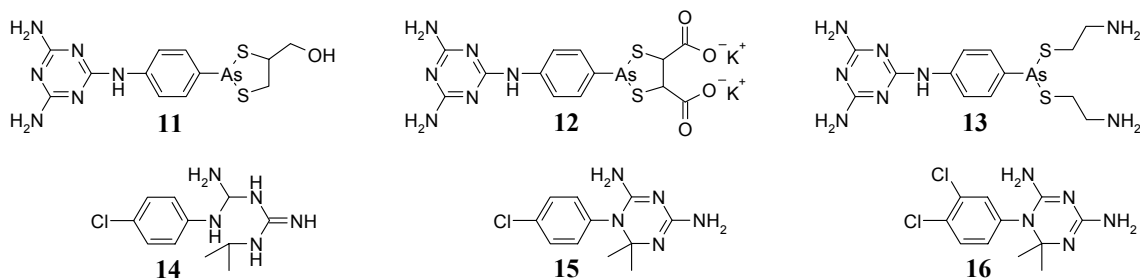
Triazine dyes are not limited to use in the dyeing of fabrics and fibers, but have also found extensive use in protein purification.<sup>76</sup> Dextran conjugates of the triazine dye Cibacron blue F3GA used to measure the void volume in gel filtration chromatography were found to selectively interact with some proteins during chromatography. In 1968 the dye portion of the conjugate was demonstrated as the portion of the molecule responsible for the interaction. Since the early 1970's triazine dyes have been used as affinity absorbents in the purification of a wide variety of proteins.<sup>77</sup> The triazine ring is used to affix the various dyes to different support matrices.

#### 1.6.5 Triazine drugs

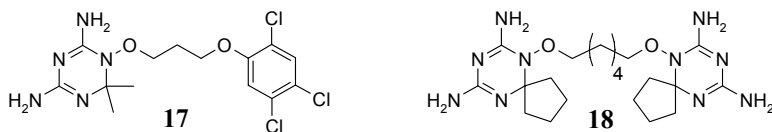
Triazines are found as components of some therapeutically useful drugs. Much of the initial efforts of triazine chemists were toward the production of medicinally useful compounds, resulting in active compounds for the treatment of cancer and malaria. Friedheim began research in the mid 1940's on the use of triazines in the synthesis of therapeutic agents for treatment of parasites,<sup>78</sup> producing arsenic and antimony containing substituted melamines, some of which are still in use today.

### 1.6.5.1 Triazine drugs for parasites

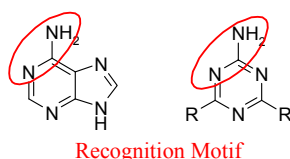
Melarsoprol (**11**) was one of Friedheim's initial discoveries for the treatment of parasites and was introduced in 1947.<sup>79</sup> More water soluble forms have been developed including Melarsonyl (**12**) and Melarsamine (**13**), but as can be imagined these compounds have the risk of inducing arsenic poisoning. Another antiparasitic drug introduced in the late 1940's was proguanil (**14**), which is converted to the active metabolite cycloguanil (**15**), which contains a triazine. Knowing that cycloguanil was a pharmacologically active metabolite lead to its use in treating malaria, as well as the synthesis of analogs such as chlorproguanil and its active metabolite chlorcycloguanil (**16**). The triazines belong to the class of antiparasitic compounds known as antifolates. They loosely resemble folate, and act as inhibitors of dihydrofolate reductase resulting in the inhibition of DNA synthesis.



The development of antiparasitic agents based on the triazine moiety has continued at a steady pace, with multiple new potential drugs identified. Two of these include WR99210 (**17**) and SIPI1029 (**18**). One advantage of using triazines in the production of antiparasitic compounds, specifically those causing malaria and African sleeping sickness is the affordability of the building blocks and the ease with which such drugs can be produced. The need for such drugs is generally highest in resource-poor settings; therefore cost is an important issue in developing drugs for such a market.



A unique route for treatment of such diseases as African sleeping sickness was investigated using triazines,<sup>80</sup> which offer a recognition motif similar to adenine for a unique nucleotide transporter in trypanosomes (Figure 1.10).<sup>81</sup> Various substituted triazines were appending to polyamines, which are toxic to trypanosomes, to investigate the selective delivery of these toxic agents to parasites.



**Figure 1.10.** Common adenine receptor recognition motif.

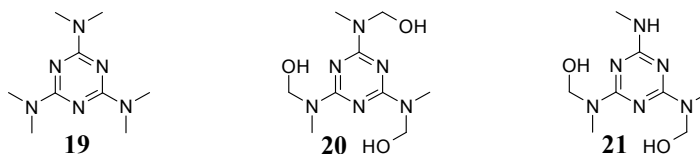
#### 1.6.5.2 Triazine drugs in cancer treatment

Hexamethylmelamine (HMM, **19**) is an antitumor agent that was discovered in the early 1950's,<sup>82</sup> and showed limited activity against murine tumor models. It was introduced into the clinic in 1965, even though the antitumor effects were described as marginal.<sup>83</sup> HMM showed subsequent and significant solid antitumor activity which propelled it into clinical use, where it is still used today (Hexalin, altretamine). The mode of action is known to include the *in vivo* *N*-demethylation of HMM via a P450 mediated pathway, which occurs rapidly in the liver.<sup>84</sup> Significant antitumor activity is mediated by *N*-hydroxymethyl intermediates. Knowing the active biological intermediate has lead to the development of various analogs of HMM.

Trimelanol (TM, **20**) was a promising alternative due to its increased water solubility, and was selected for clinical trials. The formulation of TM presented a problem as upon standing a white precipitate would form that was apparently due to polymerization of the compound. The difficulties with formulation of TM could not be overcome leading to the suspension of clinical studies.<sup>85</sup>

In the search for more stable and active analogs of TM, the compound denoted CB7646 (**21**) was discovered.<sup>86</sup> It has one less hydroxymethyl group and this modification appears to decrease the polymerization problems associated with TM, while increasing the water solubility.



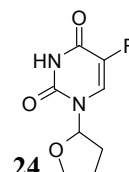
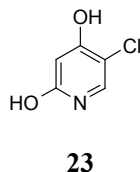
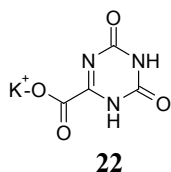


The mode of action of methylmelamines is thought to occur by forming covalent adducts with DNA and the possibility of forming DNA-interstrand crosslinks, and DNA-protein crosslinks. However, *in vitro* tests for the alkylating activity of HMM and its metabolites have been negative. These drugs have found added value in the treatment of drug-resistant tumors, specifically tumors resistant to platinum drugs.

Another early application of triazine drugs in cancer treatment was a result of the isosteric replacement of carbon by nitrogen at the C-5 position of the nucleotide cytidine. 5-Azacytidine (**3**) was synthesized first in 1964, and found two years later in bacterial ferments (*vide supra*).<sup>87</sup> The incorporation of 5-azacytidine into DNA inhibits its methylation, and DNA-methyltransferase becomes irreversibly bound to the azacytosine residue.<sup>62</sup> Methylation of DNA is involved in gene regulation, and many cancers show increased or decreased levels of DNA methylation in relation to healthy cells. 5-Azacytidine has shown clinical efficacy in treating cancers such as metastatic lung cancer.<sup>88</sup> Nucleotide analogues have also been pursued as antagonists for the P2Y receptor for potential therapeutic applications in the cardiovascular and endocrine system.<sup>89</sup>

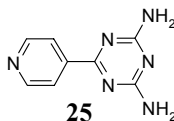
Potassium oxonate (Oxo, **22**) has found use in a combination treatment of cancer with 5-fluorouracil (5-FU). The mode of action requires the bioactivation of 5-FU, as 5-FU is not by itself cytotoxic. The end result is the inhibition of the enzyme thymidylate synthase, the only route of *de novo* thymidylate for DNA synthesis. To offset the rapid degradation of 5-FU by the liver, it is combined with 5-chloro-2,4-dihydroxypyridine (CDHP, **23**), an inhibitor of the enzyme responsible for 5-FU degradation, thus allowing prolonged retention of effective concentrations of 5-FU in the blood. One side effect of increased 5-FU levels is an increase in gastrointestinal (GI) toxicity. Toxicity occurs from the phosphorylation of 5-FU in the GI mucosa resulting in a potent cytotoxic effect on the rapidly growing cells lining the GI tract. The inclusion of Oxo inhibits the enzyme responsible for the phosphorylation of 5-FU in the GI tract without any loss of antitumor activity, thus decreasing GI tract cytotoxicity.<sup>90</sup> The formulation

of Oxo (**22**) in combination with CDHP (**23**) and a prodrug of 5-FU known as FT (**24**), in a ratio of 1-Oxo:0.4-CDHP:1-FT, is known as S-1.<sup>91</sup> This formula was developed and passed preclinical trials in Japan, and recently underwent a Phase I clinical trial in the United States.<sup>92</sup>



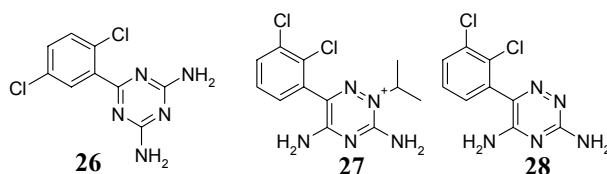
S-1 Ratio = 1 : 0.4 : 1

The series of compounds containing the 6-aryl-2,4-diamino-1,3,5-triazine chemotype show a variety of biological activities. They show antimicrobial activity (*vide supra*), and a recent investigation demonstrated the therapeutic potential of 2,4-diamino-6-(pyridine-4-yl)-1,3,5-triazine (4PyDAT, **25**) using a metastatic tumor model. The compound was administered orally, and had a moderate antimetastatic and antitumor activity, without toxicity to the host. The production of urokinase-type plasminogen activator was significantly inhibited by 4PyDAT, leading to the hypothesis that inhibition of angiogenesis may be responsible for the antimetastatic and antitumor effects, rather than directly acting in an antiproliferative manner on the tumor cells.<sup>93</sup>

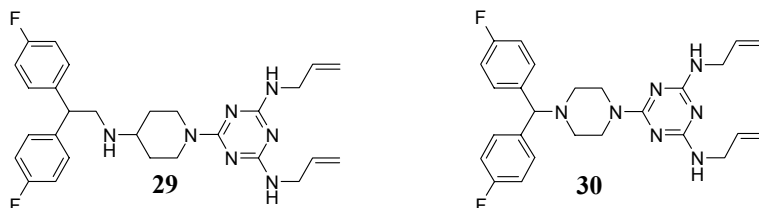


Irsogladine (**26**), also containing the 6-aryl-2,4-diamino-1,3,5-triazine chemotype, is a triazine containing anti-inflammatory drug also used in the treatment of ulcers. It was recently found that modulation of NO synthesis contributes to the gastroprotective effects of irsogladine.<sup>94</sup> Irsogladine was investigated for the inhibition of cell proliferation and tubular

morphogenesis of vascular endothelial cells. Irsogladine was found to significantly inhibit tumor growth of human glioma cells in mice, showing signs of angiogenesis inhibition.<sup>95</sup> Structurally related compounds, but containing the 1,2,4-triazine ring are Lamotrigine (**27**), an antiepileptic drug,<sup>96</sup> and BW-A256C (**28**) used as an antiarrhythmic agent.<sup>97</sup>

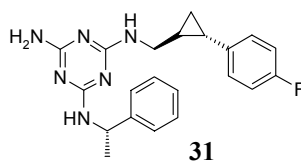


The compound S9788 (**29**) developed by Servier Laboratories is being pursued as a multidrug-resistance (MDR) reversal agent.<sup>98</sup> The dipropenylpiperidyl-1,3,5-triazine does not belong to any class of known MDR reversal agents. MDR is a result of the over expression of the *mdr1* gene, resulting in the production of the multidrug transporter P-glycoprotein. The P-glycoprotein acts as an ATP-dependent drug-efflux pump, reducing the intracellular accumulation of certain drugs. The compound S9788 was shown to be more effective than verapamil, the standard MDR reversal agent, in sensitizing MDR cell lines *in vitro*.<sup>99</sup> It has been tested in a limited Phase I clinical trial with co-administration of doxorubicin.<sup>100</sup> A related structure to S9788, marketed by the same company, is the drug almitrine (**30**), which is used in the treatment of oxygen deficiency.



### 1.6.6 Potential triazine containing drugs

One of the driving forces for utilizing triazines in drug discovery is the ability to rapidly construct a large number of compounds and further conduct structure-activity relationship studies. Three different moieties can easily be placed around the triazine core. The abundance of available amine nucleophiles for attachment to the triazine allows a survey over a wide area of the chemical landscape. This method has lead to the synthesis and screening of compounds containing the triazine ring for a variety of different and unrelated conditions. The first efforts for finding medicinally relevant triazine compounds were directed towards antimalarials and this continues as an active endeavor.<sup>101</sup>

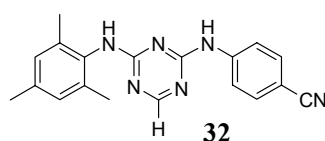


Aryl-substituted triazines were found to have antidepressant activity in the 1960's.<sup>102</sup> Bristol-Myers Squibb recently patented several triazines as 5-HT<sub>7</sub> receptor antagonists.<sup>103</sup> Compound **31** showed a dose dependent and significant suppression of rat pup vocalization, a reliable method for detecting potential antidepressants.<sup>104</sup> An emerging route to the treatment of depression involves the development of inhibitors for the corticotrophin-releasing factor (CRF) receptor. Hypersecretion of CRF has been linked to depression and affective disorders, and elevated levels of cortisol have been documented in many depressed patients. Several triazine analogs were shown by researches at Bristol-Myers Squibb to have high affinity for the CRF receptor.<sup>105</sup>

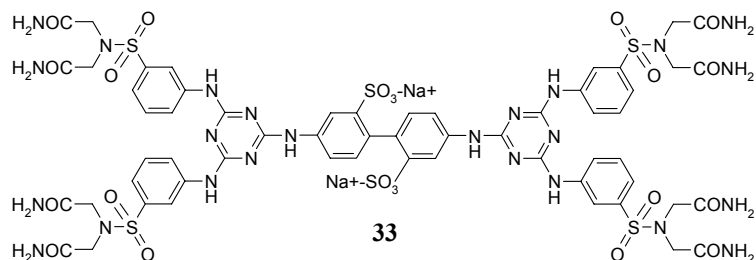
Triazine containing inhibitors of dihydrofolate reductase in the treatment of human cancer have also been investigated.<sup>106</sup> Inhibitors of the ester transfer protein for potential use in treating atherosclerosis have been identified which contain triazines.<sup>107</sup> These compounds work through inhibition of the enzyme responsible for transferring cholesterol from HDL to LDL. Inhibitors of estrogen-modulated transcription factor activation containing triazines have been

identified.<sup>108</sup> Inhibitors of inosine monophosphate dehydrogenase, with potential in the treatment of autoimmune disorders, were synthesized from cyanuric chloride.<sup>109</sup> Nucleoside analogs, some of these containing triazines, have found efficacy in treating cancer and viral infections. Triazine containing ATP analogs have been investigated as inhibitors of DNA gyrase, with potential use as antibiotics. A trisubstituted triazine was also found to be an effective DNA gyrase inhibitor.<sup>110</sup>

Non-nucleoside reverse transcriptase inhibitors for treatment of HIV infections were first discovered upon screening of Janssen Pharmaceutica's compound library in 1987.<sup>111</sup> Diaminotriazine (DATA, **32**) containing compounds were found to be very potent, but have been replaced by diarylpyrimidine analogues which show better activity against some emerging resistant double mutant HIV strains.

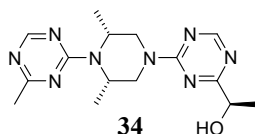


A unique anti-viral compound that has found laboratory efficacy in the treatment of human respiratory syncytial virus (RSV) contains a dendrimer-like structure and two triazines. Wyeth-Ayerst found the compound RFI-641 (**33**) from a structure activity relationship study utilizing an initial hit identified from a high-throughput whole virus cell-based assay of 20,000 compounds.<sup>112</sup> The compound works by inhibiting the fusion of the virus to the target cell. Compound **33** is not viricidal and exerts its effects through disruption of virus-cell interactions.



Resistance to macrolide antibiotics occurs through base-specific methylation of the bacterial 23S ribosomal RNA near the macrolide binding site. Methyltransferases which are responsible for this site specific modification belong to the Erm family. An NMR-based screening method was used to identify a series of triazine-containing compounds that bind weakly to ErmAM.<sup>113</sup> Initial lead compounds were further optimized using parallel synthesis to construct 411 new triazine compounds, some of which inhibited the methylation of rRNA in the low micromolar range. Further NMR and X-ray studies were carried out and revealing the inhibitors bind to the Erm protein at the S-adenosylmethionine binding site. These triazine compounds represent novel methyltransferase inhibitors.

Treatment of diabetes may soon benefit from novel triazine based sorbitol dehydrogenase (SDH) inhibitors. Mylari and coworkers constructed a family of novel triazine containing compounds, assaying them for inhibition of SDH. Under instances of increased flux of sorbitol through the SDH enzyme, like conditions present in persons with diabetes, an imbalance in the cytoplasmic  $\text{NAD}^+/\text{NADH}$  ratio is created. It has been reported that inhibition of SDH can help restore the altered  $\text{NAD}^+/\text{NADH}$  ratio. The best compound, **34**, was orally active and quite potent.



Patents abound on current efforts to utilize triazines in the identification of pharmaceutically active compounds. Multiple new targets and potential triazine based therapeutics have emerged since 1981 when the last review of drugs in the 1,3,5-triazine series was published in a Russian journal.<sup>114</sup>

#### *1.6.6.1 Triazine drugs by combinatorial methods*

Many researchers have used triazines in the construction of combinatorial libraries.<sup>115</sup> Combinatorial methods used in conjunction with screening methods utilizing zebra fish have identified novel triazine compounds which destabilize microtubules.<sup>116</sup> A similar combinatorial

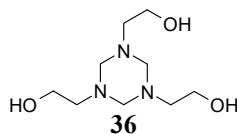
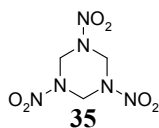
method was utilized in the construction of a library containing 1536 triazine compounds. A zebra fish embryo screening methodology was utilized; identify small molecules which induce a unique or novel phenotype.<sup>117</sup> Combinatorial methods have also been used to construct libraries for the potential identification of lead compounds for treatment of malaria.<sup>101</sup>

The largest triazine library synthesized to date included 46,656 individual triazine compounds and was utilized in screening for novel antimicrobials.<sup>118</sup> Beads containing the triazine compounds were placed on a plate of agar. Photolysis of the photocleavable linker released the triazine molecules. A 'lawn' of bacteria was then plated on the agar with active compounds identified by a white zone around a given bead. Beads found in a region of no bacteria growth were isolated from the agar plate. The beads were encoded using secondary amine tagging,<sup>119</sup> and thus the chemical history for each bead and the corresponding structure of the triazine could be identified. The compounds identified were only moderately active, but the approach identified unique structures not previously considered as antimicrobial agents.

#### *1.6.7 Triazine explosives and industrial applications*

Nitro derivatives of 1,3,5-triazines can be formed and are used and investigated as high-energy compounds.<sup>120</sup> The best known nitro-triazine derivative is RDX (**34**), a high density explosive with good thermal stability. The first investigations using RDX was as a therapeutic agent in 1899. In 1920 RDX was recognized as a possible explosive, and later used during the Second World War by both sides by mixing it with TNT (trinitrotoluene) to create more powerful bombs and shells.

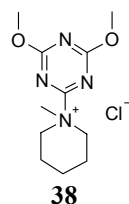
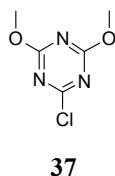
The triethanol triazine **36**, has found industrial use as a reagent for the removal of sulfur compounds from natural gas streams. Triadine 3 is the trade name for **36** marketed as a biocide for the treatment of water based machining fluids, and also as an antiseptic.



### 1.6.8 Academic exploration of triazines

#### 1.6.8.1 Triazines as condensing reagents

Academic uses of cyanuric acid are plentiful. Triazines have found extensive use as condensing reagents.<sup>121</sup> The simplest condensing reagent is cyanuric chloride, which upon reaction with a carboxylic acid produces an acid chloride.<sup>122</sup> Trifluorotriazine has also been used to produce crystalline acid fluorides of amino acids. The reagent 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **37**) has found extensive use as an activating reagent. The use of CDMT requires a tertiary amine, *N*-methylmorpholine (NMM) being the most commonly amine employed. Activation is thought to occur *in situ* by substitution of the monochlorotriazine by the amine. Addition of NMM to CDMT gives the reactive 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**38**) which is used directly as an activating agent.<sup>123</sup> These triazine condensing reagents show less epimerization than other coupling reagents and are useful in the formation of esters and are efficient in the coupling of sterically hindered substrates.



Chiral triazine derivatives have been utilized in the synthesis of peptides starting with racemic substrates.<sup>124</sup> Other chiral substituted triazines have been synthesized as chiral discriminators and for use as chiral auxiliaries in High Performance Liquid Chromatography (HPLC).<sup>125</sup>

The immobilization of condensing reagents simplifies the reaction work up. Triazine condensing reagents have been immobilized on solid supports.<sup>126</sup> Solid-supported triazines have also found use as nucleophilic<sup>127</sup> and proton scavengers<sup>128</sup> for use in solid phase organic synthesis.



### 1.6.8.2 Triazines in functional group manipulations

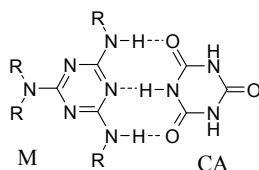
Triazines have found extensive use as reagents in the conversion of functional groups. As discussed previously they have found use in the activation/modification of carboxylic acids.<sup>121</sup> Additional unique uses have been developed and refined by research conducted at the Università degli Studi di Sassari in Italy. Using sodium borohydride and cyanuric chloride the reduction of carboxylic acids to alcohols under mild conditions was demonstrated.<sup>129</sup> Primary alcohols were obtained in the range of 70-90 percent yield, and the method was compatible for use with protected amino acids. Using the condensing reagent CDMT (**37**) activated with NMM carboxylic acids were converted to aldehydes or alcohols using H<sub>2</sub> and Pd/C.<sup>130</sup> Weinreb amides were produced using CDMT and NMM in combination with *N,O*-dimethylhydroxylamine.<sup>131</sup> Hydroxamates were formed using CDMT/NMM and a suitably protected hydroxylamine (*O*-benzyl- or *tert*-butyldiphenylsilyl-).

Ketones were produced from *N*-protected amino acids using CDMT/NMM and Grignard/CuI reagents.<sup>132</sup> The mild and chemoselective oxidation of alcohols to aldehydes or ketones using 1,3,5-trichloro-2,4,6-triazinetriene (trichloroisocyanuric acid) in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) occurred nearly quantitatively on multi-substrates in 20 minutes. The oxidation of primary alcohols occurred more rapidly than secondary, and the method was extended to the selective oxidation of a primary alcohol in the presence of a secondary alcohol.<sup>133</sup> Cyanuric chloride was also shown as an activating agent of DMSO in the classical Swern oxidation of alcohols.<sup>134</sup> The conversion of primary, secondary, and tertiary alcohols to the corresponding alkyl chloride occurs in high yields on a variety of substrates using cyanuric chloride in the presence of DMF.<sup>135</sup> The selective protection of primary alcohols by formation of the formate ester occurs in the presence of cyanuric chloride and DMF with the addition of LiF, followed by the addition of water.<sup>136</sup> The Beckmann rearrangement of ketoximes to the corresponding amides was conducted using cyanuric chloride in DMF, generally in high yields.<sup>137</sup>

### 1.6.8.3 Triazines in molecular recognition, supramolecular, and materials chemistry

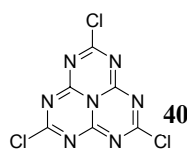
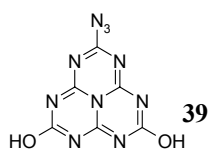
Triazines can be used in the construction of novel supramolecular constructs held together through hydrogen bonding. Melamine (M) and the oxo-tautomer of cyanuric acid (CA) have complementary hydrogen bonding patterns (Figure 1.11), and when mixed in aqueous

solutions form a stable 1:1 complex which can be heated to 450 °C without change.<sup>138</sup> The complementary hydrogen bonding between M:CA has been used in the construction of such macromolecular assemblies as ‘rosettes’,<sup>139</sup> polymeric rods,<sup>140</sup> and tapes;<sup>141</sup> Whitesides and coworkers pioneering the work.<sup>142</sup> Reinhoudt has constructed and characterizing an enantiomerically pure M:CA hydrogen-bonded assembly,<sup>143</sup> and recently reviewed the field of noncovalent synthesis, including M:CA constructs.<sup>144</sup>

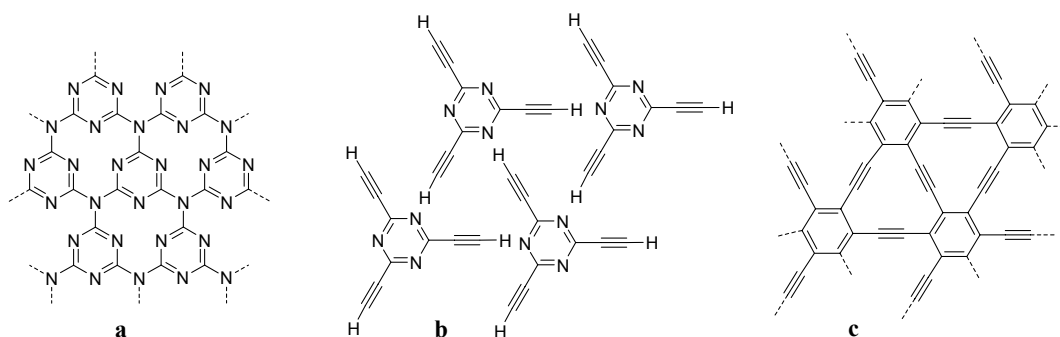


**Figure 1.11.** Schematic representation of a melamine:cyanuric acid (M:CA) dimer.

Linus C. Pauling not only left behind a chemical legacy, he also left behind a chemical mystery. Found on the blackboard in his office after his death was the unique structure **39**, a molecule unknown at that time,<sup>145</sup> containing a tri-*s*-triazine (other names include: *s*-heptazine and cyamelurine). The reason for Pauling’s interest in the molecule and why it was on his board remains a puzzle, although theories abound.<sup>145b</sup> Perhaps due to Pauling’s mystery molecule or just the intrinsic uniqueness of the tri-*s*-triazines several groups have pursued their syntheses. Several tri-*s*-triazines have been synthesized, including the cyanuric chloride analog **40**, later used in the construction of novel macrocycles.<sup>146</sup> Macrocycles have also been constructed containing the smaller *s*-triazine, and host-guest chemistry investigated.<sup>147</sup> Triazines coupled together with piperazine were used to construct novel heteromacrocycles. The ability of these macrocycles to encapsulate and recognize sugars was investigated. The triazo-tri-*s*-triazine, containing an azide at each apical carbon, has recently been prepared and found to be a stable precursor for the production of nitrogen-rich materials.<sup>148</sup>



Considerable research efforts have been devoted to the synthesis of carbon nitride,  $C_3N_4$ , networks (Figure 1.12a). These unique materials have the potential for high-performance materials possessing hard, lightweight, and thermally stable properties. Nitrogen rich materials are derived from the thermal decomposition of compounds containing an equal to low carbon:nitrogen ratio. Triazines, specifically those substituted with amines, hydrazines, and azides, have found particular application in this area.<sup>149</sup> Novel one-dimensional hydrogen bonded arrays (Figure 1.12b) analogous to the hypothetical carbon allotrope graphyne (Figure 1.12c) have also been constructed using triazines.<sup>150</sup>



**Figure 1.12.** Novel triazine based materials. a) Hypothetical depiction of the ‘fully densified’ graphitic phase of  $C_3N_4$ . b) Atomic representation of extended hydrogen-bonded triazine array, similar to c) the hypothetical carbon allotrope ‘graphyne’.

## 1.7 Triazine Dendrimers<sup>▽</sup>

### 1.7.1 The 20<sup>th</sup> century

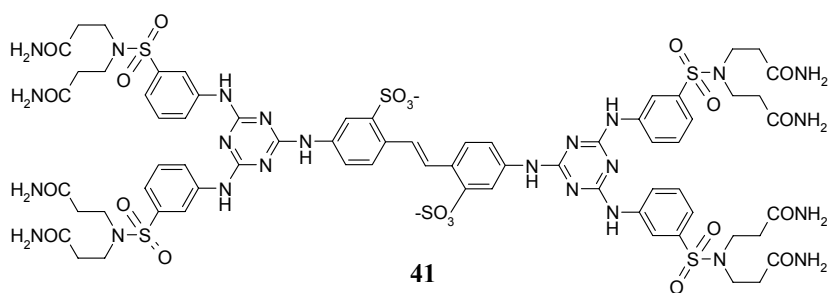
The first examples of dendrimers containing triazines are found in patents.<sup>151</sup> The first extensive document concerned specifically with the construction of dendrimers by substitution of cyanuric chloride is a 1997 German patent.<sup>151d</sup> The dendrimers described therein were constructed through both divergent and convergent methods using diamine linkers. The appearance of triazines in dendrimers next surfaced in an extended abstract submitted to the Polymeric Materials Science and Engineering division for the Fall 214<sup>th</sup> national American

<sup>▽</sup> Schemes outlining the syntheses of all the dendrimers referred to in this section and a complete listing of the references in chronological order are given in Appendix A.

Chemical Society meeting.<sup>152</sup> Fréchet demonstrated the self assembly of higher ordered dendrimer structures by attaching two complementary hydrogen bonding moieties to the focal point of the dendrons. Melamine and cyanuric acid were separately appended to generation 2-4 dendrons, and the supramolecular assembly of these dendrons with each other was investigated. Generation 2 dendrons formed the expected hexameric structure from the complementary hydrogen bonding of the melamine and cyanuric acid, but solutions of the larger dendrons appeared to be an equilibrium mixture of different aggregates.

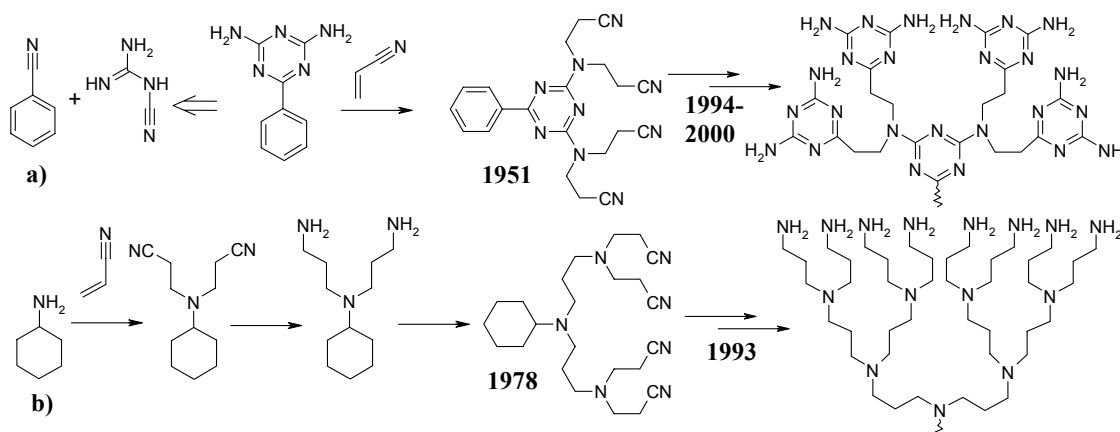
The first research paper to report the incorporation of a triazine in a dendrimer was published in 1998.<sup>153</sup> The dendrimer was only of generation one (G1), but the attachment of six surface groups to the triazine branching units through silyloxy phthalocyanine linkages was unique.

In 1992 Wyeth-Ayerst initiated a program to identify novel inhibitors of the human respiratory syncytial virus (RSV).<sup>154</sup> The only active compound found from screening 20,000 compounds using a whole virus and cell based assay was a dendrimer like structure. The identified compound termed CL 309623 (**41**) contains a disulfonated stilbene core linked at each end to a triazine. The compound was originally synthesized in the 1960's by the American Cyanamid Organic Chemicals Division as a potential optical brightener (see Figure 1.8). A patent was filed in 1997 for use of CL 309623 and similar derivatives for the treatment of viral infections.<sup>151e</sup> In 1998 a comprehensive structure-activity relationship study was undertaken, identifying even more potent molecules.<sup>155</sup> Further structure-activity relationship studies conducted in 2001 identified the lead molecule RFI-641 (**33**) as a potent and selective inhibitor of RSV. It has been determined these dendrimer like compounds interrupt the F-protein mediated cell fusion of RSV with the target cell through specific interaction with the fusion protein of the RSV virus.



One of the more unique approaches to the construction of triazine dendrimers, and arguably the first dendrimers constructed containing a triazine, incorporates the cycloaddition of nitriles with cyanoguanidine forming a 2,4-diamine-1,3,5-triazine, commonly known as a guanamine. This work had been described in a Polish patent as early as 1994,<sup>151b</sup> referred to in reviews written by the principle investigator<sup>156</sup> and a thesis, with the first research paper on the subject published in 2000.<sup>157</sup> The corresponding author of the paper, Maciejewski, wrote one of the earliest theoretical papers on the subject of dendrimers in 1982.<sup>158</sup>

Cyanoethylation of the amines of guanamines forms a tetracyano dendron. Elaboration of the dendron through cycloaddition between the peripheral nitriles and cyanoguanidine increases the dendrimer generation (Scheme 1.1a). Cyanoethylation was the method used by Vögtle (Scheme 1.1b) in what is commonly described as the first dendrimer synthesis. A method resulting in a compound with strikingly similarities to that of Vögtle's was described in a patent by Niederhauser in 1951,<sup>159</sup> twenty-seven years prior to Vögtle's work. Niederhauser knew of the ability to reduce the nitriles to amines as he described such a method in a patent filed in 1945.<sup>160</sup> Either through reduction of the nitriles to amines (he did hydrolyze them to carboxylic acids), or further cycloaddition reactions with the nitriles and Niederhauser would have laid claim to the first dendrimer. Here was a near miss to the beginning of dendrimer chemistry.



**Scheme 1.1.** Similarities in early dendrimer construction. Route (a) involves the iterative cyanoethylation-cycloguanadylations. Route (b) involves iterative cyanoethylation-reduction reactions.

Vögtle provides very little data for his molecule containing four amines besides an  $R_f$  value from thin layer chromatography (TLC). He does observe a molecular ion peak ( $M^+$ ) for his compound containing four nitriles, but very similar compounds have been known since 1942.<sup>161</sup> Vögtle used diamines to produce molecules with eight nitriles, which were more thoroughly characterized by both TLC and mass spectral analysis. Vögtle's contribution to the evolution of dendrimer chemistry relies on the creation and definition of the term 'cascade syntheses' where he emphasized reactions could be "carried out repeatedly, whereby... a functional group is made to react in such a way as to appear twice in the subsequent molecule."

In 1993 two groups published back-to-back papers on the successful optimization of Vögtle's route<sup>162</sup> to produce true dendrimers. These methods eventually lead to the commercial production of this class of dendrimers known as poly(propylene imine) (PPI) dendrimers.<sup>163</sup> The elaboration of Niederhauser's tetracyanoethyl benzoguanamine to generation 4 dendrimer (*vide supra*), took over forty years to accomplish with the products containing some incomplete arising from incomplete cycloaddition reactions. The cycloaddition/cyanoethylation method utilized requires no functional group interconversions or the use of protecting groups.

### 1.7.2 The 21<sup>st</sup> century

The year 2000 offered five additional efforts towards the syntheses of triazine containing dendrimers, with each offering a unique approach.

Burn and coworkers used the alkoxy and aryloxy substitution of cyanuric chloride to form the surface groups of a second generation (G2) dendrimer linked by a distyrylbenzene core. The electroluminescence of this dendrimer was investigated and the molecule used in the construction of an organic light-emitting diode (OLED).<sup>164</sup>

Zhang and Simanek described methods for the construction of what are termed melamine based dendrimers using diamine linkers in the substitution of cyanuric chloride.<sup>165</sup> Unique to this method is the lack of functional group manipulations or protecting groups required in the dendrimer synthesis; this approach is discussed further in Chapter II. A third generation (G3) dendrimer was constructed by both convergent and divergent routes utilizing the chemoselective reactivity of *p*-aminobenzylamine with monochlorotriazines.

Takagi and coworkers published two papers on the syntheses of structurally related triazine dendrimers. Their first paper described the convergent synthesis of a G2 dendrimer and generation 3 dendrons (D3). The investigators substituted cyanuric chloride with the aromatic

amine of *p*-nitroaniline. Reduction of the nitro group to reveal an amine was followed by a subsequent reaction with a dichlorotriazine to increase the generation by one.<sup>166</sup> The second paper described methods for the convergent and divergent syntheses of triazine dendrimers using different linkage groups to accomplish each. The result was the synthesis of G2 dendrimers.<sup>167</sup> The divergent route described in the second paper utilized the same methodology as the convergent route outlined in their first paper.<sup>166</sup> The G2 dendrimer produced by the convergent route was synthesized starting with a single aryloxy substitution of cyanuric chloride. Subsequent generations of dendrons were achieved through the double substitution of the dichlorotriazine building block by the appropriate generation arylamine.

The synthesis of zero generation (G0) and G1 dendrimers were described in a report submitted to the Fourth International Electronic Conference on Synthetic Organic Chemistry.<sup>168</sup> The dendrimers were synthesized by the amine substitution of 2,4,6-trisphenoxy-1,3,5-triazine, but required temperatures of 260-280 °C to get complete substitution at all three positions of the triazine ring.

It should be noted that during this same time frame Kim and coworkers from the Hyperstructured Organic Materials Research Center in Korea published a series of papers on hyperbranched polymers utilizing triazines as the scaffold for the synthesis of AB<sub>2</sub> type monomers.<sup>169</sup> Hyperbranched polymers were synthesized by condensing these triazine containing monomers. However, the hyperbranched structure of these materials arose from the reaction of functional groups attached to aryl groups appended to a triazine core, and not through direct substitution on the triazine ring.

Five papers were published in 2001 describing the synthesis of dendrimers containing triazines. The first example demonstrating the solid phase synthesis of a triazine dendrimer was published by Marsh and coworkers.<sup>128</sup> Simanek and coworkers demonstrated the ability to control the composition of melamine based dendrimer through the syntheses of G3 dendrimers having one or two unique sites at the periphery amenable to post-synthetic modification.<sup>170</sup> Simanek and Zhang published a paper illustrating molecular recognition properties of novel melamine dendrimers.<sup>171</sup> Dehaen and Verheyde synthesized dendrimers containing oxadiazoles with a single triazine at the core.<sup>172</sup> Later Dehaen and coworkers produced dendrimers containing triazines as the branching units.<sup>173</sup> Their route was unique in that first anisole was substituted on the triazine ring by a Grignard reaction, giving a dichlorotriazine product. Surface groups were attached to the triazine ring through aryloxy nucleophilic displacement of the

chlorides. The methoxy functionality of anisole was unmasked to reveal a phenol, which was subsequently reacted with 0.5 equivalents of cyanuric chloride to arrive at the next generation of dendron.

The year 2002 saw the publication of only two papers describing the synthesis of triazine dendrimers. The first paper published describes the synthesis of polydentate and polynucleating *N*-donor ligands containing the triazine ring as the branching and core group of G1 dendrimers.<sup>174</sup> Simanek published another paper on the molecular recognition properties of melamine dendrimers; specifically identify trends in triazine dendrimer composition which result in the gelation of organic solvents containing melamine type dendrimers.<sup>175</sup>

In 2003 nine papers were published containing original triazine dendrimers. Simanek and coworkers were responsible for six of these publications including the syntheses dendrimers containing multiple disulfide linkages. Kinetics of disulfide exchange within the dendrimer structure were monitored, correlating the rate of exchange to the size of dendrimer.<sup>176</sup> The attachment of DNA<sup>177</sup> and peptides to melamine dendrimers were separately described,<sup>178</sup> as well as preliminary studies into melamine dendrimers as drug delivery vehicles.<sup>179</sup> New linking groups were identified for the construction of compositionally diverse dendrimers,<sup>180</sup> along with the identification of a novel organoclay morphology from the frustrated intercalation of dendritic triazine molecules.<sup>181</sup>

Other triazine dendrimers reported in 2003 include the synthesis of a fourth generation triazine dendrimer on a silica solid support.<sup>182</sup> Gamez, Reedijk and coworkers visited again the construction of triazine dendrimers containing multiple metal ligands at the surface.<sup>183</sup> A triazine library was constructed on the solid support and later screened to identify lead compounds with antibacterial properties.<sup>184</sup> A modified G2 Newkome type dendrimer with nine surface amines was constructed on the solid support; increasing the loading capacity of the resin. The surface amines were further modified to present a phenol and subsequently reacted with cyanuric chloride. This resulted in the incorporation of nine dichlorotriazines at the surface of the dendron. These were subsequently reacted with various amine nucleophiles to produce a library of compounds. The triazines were liberated from the solid support after heating the resin in the presence of morpholine or piperidine. Substitution of the aryloxy triazine bond by the secondary amine released the compound from the resin. The triazines were only located at the surface of the dendrimer, and done as a way to increase the loading of the resin, not specifically for the construction of a solid supported triazine dendrimer.



Other potential triazine containing dendrimers have been reported or could be argued to be present in the literature, but appear to be hyperbranched materials,<sup>185</sup> or simply trisubstituted triazines.<sup>186</sup> Other examples of supramolecular complexes containing triazines are found but how to classify them is more ambiguous.<sup>187</sup> A patent issued in 2000 to Isis Innovation Limited describes novel products for use in polymer chemistry.<sup>188</sup> Several of these compounds were simply a single triazine appended to a multifunctional reagent, such as a triazine with substituted with three bis-(1,3-dihydroxyprop-2-yl)amines, a molecule containing a total of 12 primary hydroxyls around the triazine ring. In the most generous sense such molecule could be considered G0 dendrimers. However, the patent described other constructs which could be considered G1 dendrimers, containing a triazine at the core.

### *1.7.3 Future possibilities*

Triazine chemistry offers access to a multitude of useful molecules, from medicinal chemistry to materials. The use of triazines in dendrimer syntheses offer access to unique and tailored molecules possessing: multiple functionality (Chapters II and III), unique structural properties (Chapters II and IV), and for potential applications (Chapter V).

## **1.8 Conclusion**

The journey is now complete. In roughly two centuries polymers emerged from the early work of Faraday and Berzelius through somewhat difficult times to molecules of much interest and use. The study of polymers developed a rigorous science, full of theories and models to better comprehend the macromolecular realm. The emergence of polymer chemistry from under organic chemistry is a journey littered with missteps and bad ideas. Those brave enough or wise enough to pursue the idea and characterization of large molecules have been amply rewarded and offered historical immortality in the annals of chemistry through distinction of winning the Nobel Prize. It would take both hands and most of ones toes to count the winners of The Prize who achieved this distinction through working with polymers. The names most easily recognized include Staudinger, Flory, Ziegler, Natta and the recent additions of Heeger, MacDiarmid, and Shirakawa, whose direct work on polymers was responsible for them receiving The Prize. However, multiple others received their award for efforts in understanding the atomic structure and function of natural macromolecules. Sanger earned two awards by developing methods to determine the sequence of the natural copolymers. The

synthesis of the natural polymers, either in solution, on the solid phase, or using the polymerase chain reaction resulted in several Prizes. Those who discovered analytical methods by which to better characterize natural polymers have been amply awarded this singular distinction. Finally, those who have extended efforts to understand how nature uses these macromolecules and polymers, and the mechanisms by which they operate have not gone unnoticed. If the Nobel Prize is any measure of what can be deemed important in chemistry, polymers must be near the top of the list (see Appendix A for a list of Nobel Prize winners who's work dealt in some fashion with polymer chemistry, page 144).

The pursuit of novel atomic architectures is no longer just the domain of total synthesis. Polymer chemists have succeeded in mimicking nature's production of macromolecules, including composition, atomic connectivity, and stereoarrangement, and are currently pursuing novel molecular architectures. Novel macromolecular architectures are now abundant and pursued in earnest; the future prospects limited only by the imagination of the investigator. Polymer chemistry, at first misunderstood, is now a science sprouting branches of subdisciplines, dendrimer chemistry being one.

## CHAPTER II

### CHEMOSELECTIVE SYNTHESIS OF A LAYERED TRIAZINE DENDRIMER WITHOUT FUNCTIONAL OR PROTECTING GROUP MANIPULATIONS\*

#### 2.1 Introduction

The stepwise synthesis of a dendrimer is labor intensive and several drawbacks limit their commercial and academic application and production. Dendrimer syntheses by divergent methods typically employ a large excess of reagent at each step to ensure the complete modification of the multiple peripheral groups. The excess reagent employed may be recovered and recycled, but this is often impractical in academic pursuits. Divergent routes tend not to be atom economical, as only a small percentage of the atoms used for the dendrimer synthesis are incorporated into the final product. In both convergent and divergent methods functional group manipulations, including the removal or installation of protecting groups, are required. Often activating agents must be utilized to effect the coupling of monomers for dendrimer growth. Every additional step contributes to the time, effort, and ultimately cost of producing a dendrimer. Routes which limit the number of synthetic steps, while allowing rapid access to large dendrimers are attractive.

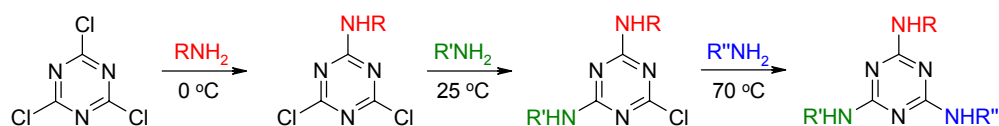
A variety of methods have emerged which reduce the number of steps and reagents used in dendrimer syntheses. Notable efforts include orthogonal routes which limit the number of functional group manipulations required.<sup>189</sup> The use of a ‘hypercore’ approach involves the coupling of convergently synthesized dendrons to a dendritic core containing multiple groups at the periphery and one or more generations of branching.<sup>190</sup> The hypercore approach is a hybrid method, combining the convergent synthesis of advanced generation dendrons with coupling to a core containing multiple groups at the periphery in a divergent manner. In 1995 Moore and coworkers devised another method taking advantage of both divergent and convergent techniques.<sup>191</sup> The method was dubbed the ‘double exponential dendrimer growth’ method. Monomers with orthogonally masked focal and surface functionalities are subject to a three step

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sequence involving dendron activation, monomer activation, and coupling; a route which doubles the dendrimer generation after completion of the three step sequence.<sup>192</sup> One-pot multi-step reaction sequences are attractive routes for the production of dendrimers while limiting the need for purification of intermediates.<sup>193</sup>

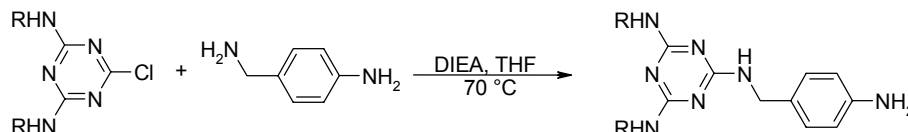
One unique aspect of triazine chemistry is the ability to control the degree of substitution on the triazine ring. Controlled substitution has been utilized as an efficient method for the construction of melamine dendrimers. The most efficient route for selective substitution of the triazine ring utilizes temperature controlled nucleophilic aromatic substitution of a trihalotriazine. Substitution by an amine nucleophile on the triazine ring of cyanuric chloride increases the electron density of the aromatic system. Subsequent substitutions on the ring require a greater energy of activation, and thus a longer reaction time or an elevated reaction temperature. The general rule: is the first substitution on cyanuric chloride by a primary amine nucleophile occurs in minutes at 0 °C, while the second substitution occurs in 12-24 hours at room temperature. The third substitution typically occurs in 12-24 hours at 70 °C (Scheme 2.1). These rules have been attributed to early studies by Moffat through his work on the syntheses of small triazine libraries to identify potential antimalarials.<sup>194</sup> These trends are not stringent and indeed the choice of solvent, the concentration of reactants, and most importantly the nature of the nucleophile greatly affect reaction rates. For example, cyclic secondary amines, such as piperidine, substitute all three positions of cyanuric chloride rapidly at room temperature, resulting in a triaminotriazine.



**Scheme 2.1.** Temperature controlled substitution of cyanuric chloride. The first substitution occurs rapidly while the reaction is cooled in an ice bath. The second reaction typically occurs overnight at room temperature. The third reaction requires elevated temperatures and 12-24 hours for the reaction to proceed to completion.

The synthesis of melamine dendrimers relies on the iterative reactions of cyanuric chloride with diamine linkers. The degree of substitution on the triazine core is controlled by the

temperature of the reaction and stoichiometry of the amine employed. Selective mono-substitution is achieved through addition of one equivalent of an amine to an ice-bath cooled solution of cyanuric chloride, giving rise to a dichlorotriazine intermediate. Subsequent reactions are likewise controlled by the temperature of the reaction and the equivalents of nucleophile used. Judicious selection of diamines affords chemoselective routes to melamine dendrimers. For example the benzylic amine of *p*-aminobenzylamine (*p*ABA) preferentially reacts with monochlorotriazines (Scheme 2.2) to yield an aniline which can subsequently react to yield the next dendrimer generation. This linker has been used in the construction of dendrimers by both convergent and divergent routes.<sup>165</sup>



**Scheme 2.2.** The chemoselective substitution of a monochlorotriazine by *p*ABA. Only the product corresponding to substitution of the triazine ring by the benzylic amine is observed.

While the choice of *p*ABA was based on experimental experience, it could have been the result of a rationale search. Indeed a small set of competition reactions were conducted to identify general nucleophilic trends in the substitution of a monochlorotriazine, and rationally identify bifunctional linkers with similar differential reactivity between the functional groups as found in *p*ABA.

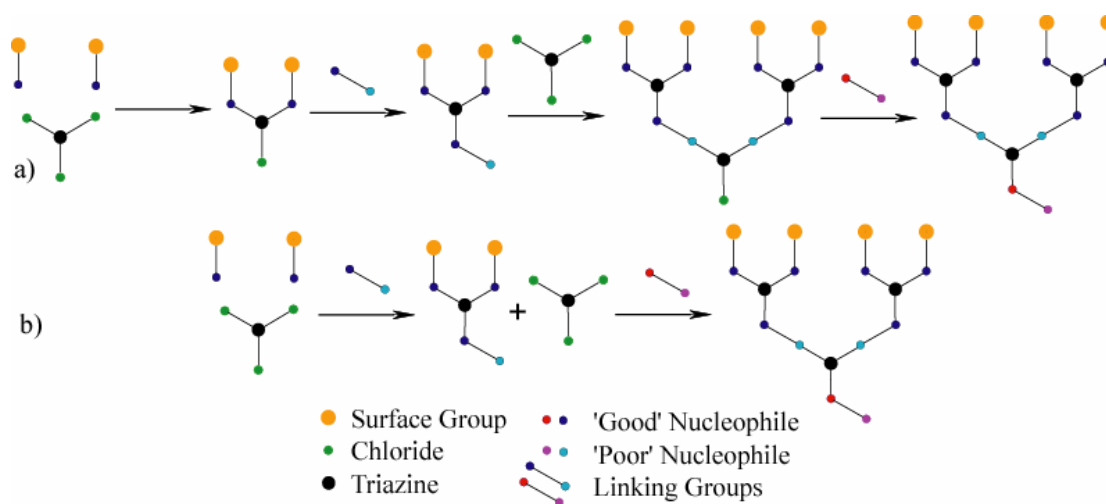
## 2.2 Rationale

Routes for melamine dendrimer syntheses can proceed in a one-generation per pot (OGPP) approach, accomplishing multiple reactions in a single flask, using chemoselective linkers. There is no need for protecting groups or functional group interconversions. Chemoselective routes for melamine dendrimer construction provide an attractive method for reducing the number of synthetic steps and reagents required in a dendrimer synthesis. The only atoms not incorporated into a melamine dendrimer during synthesis are the byproduct HCl, and the base used to scavenge it. These routes are therefore atom economical. It is the use of

temperature selective substitutions, one-generation per pot, and the utility of chemoselective linkers which make compositionally diverse dendrimer architectures readily tractable.

### 2.2.1 The one-generation per pot method

The OGPP method reduces the number of intermediates requiring purification by conducting multiple reactions in a single flask (Scheme 2.3). The typical convergent approach installs the surface groups by reacting two equivalents of the desired molecule containing a reactive nucleophile, generally a primary or secondary amine, with cyanuric chloride. After completion of the reaction the resulting monochlorotriazine is purified, characterized, and subsequently reacted with an appropriate linker, generally a diamine (Scheme 3a). The reactions are conveniently monitored by TLC, and completion is noted by the disappearance of the UV-active spot corresponding to the starting material and appearance of a single new spot.



**Scheme 2.3.** Outline of convergent dendrimer syntheses routes. a) The intermediate is purified and characterized at each stage, the result being a G-2 dendron from four reactions with four purifications. b) The OGPP (one-generation per pot) approach results in a G-2 dendron in four reactions with only two purifications.

The only difference between the traditional convergent route and the OGPP method is that upon completion of the first two substitutions on cyanuric chloride by the surface groups, the appropriate linker is then reacted with the monochlorotriazine in the same pot. Completion

of the third substitution is followed with purification and characterization, effectively removing a step to arrive at the same product (Scheme 2.3b). The use of homobifunctional diamines as the linker requires an excess of reagent and large dilutions to avoid dimerization of the monochlorotriazines. However, dimerization products are still evident when monochlorotriazines are reacted with 6-8 equivalents of piperazine as the diamine.

### 2.2.2 Chemoselective routes

The use of heterobifunctional diamine linkers, where one amine is more nucleophilic, and thus reacts faster with the monochlorotriazine, avoids side reactions resulting in triazine dimerization. Differential reactivity acts as a 'protecting group' for the less reactive nucleophile, as reactions occur faster at the more reactive site. The utilization of even a slight excess of diamine linker leads to selective fictionalization of the more reactive nucleophile exclusively if the difference in reactivity between the amines is large enough. Such is the case for the diamine linker *p*ABA, where only products corresponding to substitution by the benzylic amine are observed (*vide supra*). The less reactive amine remains unfunctionalized and is available for subsequent reactions, obviating the need to activate, deprotect, or manipulate the dendron functionality for further reaction.

An additional advantage of temperature selective substitution and the use of chemoselective linkers is the ability to rapidly introduce multiple functionalities around a triazine core. As depicted in Scheme 2.2 three different amines can be incorporated around a triazine core; this can be accomplished in a single pot. Therefore, it is possible to incorporate two different surface groups and the requisite linking group by conducting three successive substitution reactions on cyanuric chloride in a temperature controlled manner. Tailored dendrimers, containing multiple different functionalities at the dendrimer surface, are readily tractable utilizing such methods (Chapter III).

## 2.3 Identification of Linkers for Use in Triazine Dendrimer Construction

General nucleophilic trends in the substitution of monochlorotriazines were investigated, identifying bifunctional linkers for the synthesis of a melamine based dendrimer without the use of protecting groups or functional group manipulations. The dendrimer has a layered composition, where each generation linked through a different molecule. The target dendrimer composed of four different linking groups was constructed in a one-generation per pot route,

using chemoselective linkers, avoiding the use of protecting groups, even at the terminal hydroxyl groups, or other functional group interconversions.

### 2.3.1 Competition reactions

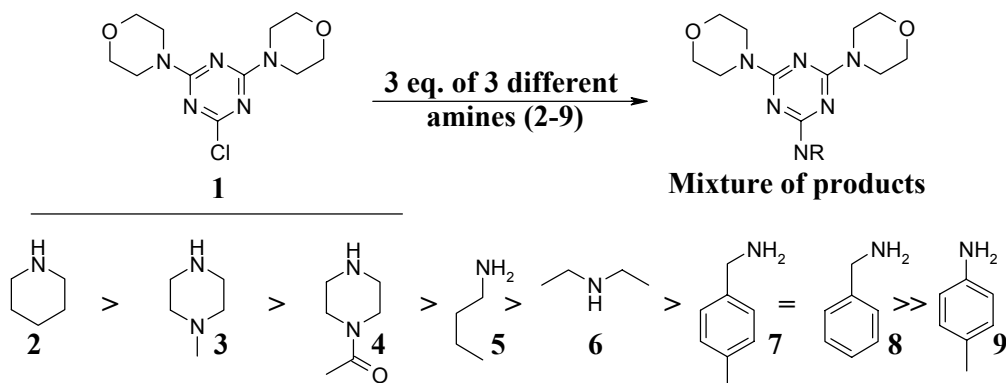
Competition experiments were conducted to determine the relative reactivity of various amine nucleophiles in reaction with a monochlorotriazine. These competition reactions were conducted in an analogous manner to methods used in polymer chemistry to determine the reactivity ratios of monomers used in copolymerizations. Reactivity ratios define the relative tendencies of two monomers to self-couple or cross-couple when used together in a copolymerization.<sup>195</sup> Monomers that have a reactivity ratio of one tend to produce random copolymers, while a ratio approaching zero suggests the monomers have no tendency to homopolymerize, and a truly alternating copolymer results. A large ratio suggests one monomer would tend to be incorporated exclusively at first, and as its concentration diminishes, the second monomer is incorporated, producing a block copolymer. To determine reactivity ratios the location and extent of incorporation into the polymer for each monomer must be determined, and NMR is currently the tool of choice.<sup>196</sup>

The competition reactions were conducted in the presence of 2-chloro-4,6-dimorpholino-1,3,5-triazine (**1**), selected both on reactivity and analytical grounds. Substitution of the triazine ring by two secondary amines strongly deactivates the triazine ring. Through deactivation of the triazine ring the subsequent third substitution depends more strongly on the nucleophilicity of the amine rather than the reactivity of the triazine. Second, morpholine has proton chemical shifts distinct from the amines utilized in the competition reactions.

Several different amines were identified containing a primary or secondary amine. Amines were also selected based on reactivity and analytical grounds. The amines (**2-9**) cover a range of reactivity and structures, from secondary amines to anilines (Figure 2.1). Substitution of an amine onto a triazine ring generally shifts the resonances of the protons  $\alpha$  to the amine downfield. For amines which have similar peak frequencies for the  $\alpha$ -protons, such as amines **2-4**, other unique chemical shifts were identified corresponding to a given amine; for example the  $\gamma$  methylene of **2**, the methyl of **3**, and the acetamide protons of **4**. The relative amount of product resulting from substitution of the monochlorotriazine by each nucleophile was determined through integration of the unique peaks corresponding to a given amine and normalizing for the number of protons present. Compounds **8** and **9** are structural isomers of each other and as such



result in substitution products with the identical mass. Amine **7** was selected for competition reactions with **9** to avoid this degeneracy.



**Figure 2.1.** Outline of competition reactions and the amines used. The general trend in amine reactivity is outlined from left to right with **2** being the most reactive.

### 2.3.2 Materials and methods

Three different amines were selected for each experiment, and 3 equivalents of each amine were dissolved in tetrahydrofuran (THF) except for the reaction conducted at 120 °C where the solvent dioxane was used. Reactions at elevated temperatures were closed and heated to ~50 °C before addition of **1**. Monochlorotriazine **1** was added to the solution containing the amines, giving a concentration 0.1 M, and then stirred for 18 hours at the desired temperature. Thin layer chromatography (TLC) confirmed the absence of any starting after 18 hours. Silica gel chromatography was used to separate the products from the excess amines. All fractions containing UV active spots that did not stain positive under use of ninhydrin were combined, followed by removal of the solvent. Analysis by NMR provided the relative ratios of products using the chemical shift of the protons  $\alpha$  to the amine or other diagnostic protons resonances.

### 2.3.3 Results

The results in Table 2.1 outline the percentage of product corresponding to the substitution by the respective amine. For each trial conducted at a set temperature three amines were selected. For example in trial 1 amines **2**, **3**, and **4** were combined with **1** and stirred at

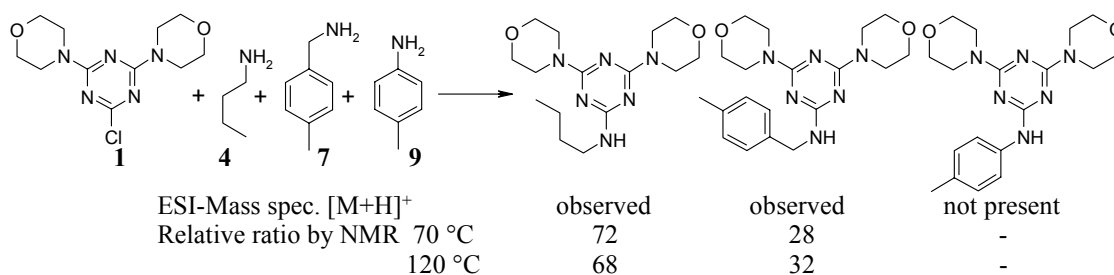
room temperature for 18 hours. A mixture of products resulted with amines **2**, **3**, and **4** determined to react with **1** in a ratio of 55:34:11. As expected an increase in reaction temperature results in a concomitant decrease in selectivity. This is apparent by comparing trials 2 and 4, where the less reactive amines are incorporated to a greater extent at elevated temperatures.

**Table 2.1.** Results from competition reactions.

Trial	Temp.	Amines	Respective yield of amine addition to <b>1</b>
1	rt	<b>2, 3, 4</b>	55:34:11
2	rt	<b>2, 5, 7</b>	98.2:1.2:0.6
3	rt	<b>4, 5, 7</b>	75:17:8
4	70	<b>2, 5, 7</b>	95.6:3:1.4
5	70	<b>4, 5, 7</b>	70:19:11
6	70	<b>5, 6, 7</b>	47:35:18
7	70	<b>5, 8, 9</b>	72:28:0
8	120 <sup>†</sup>	<b>5, 8, 9</b>	68:32:0

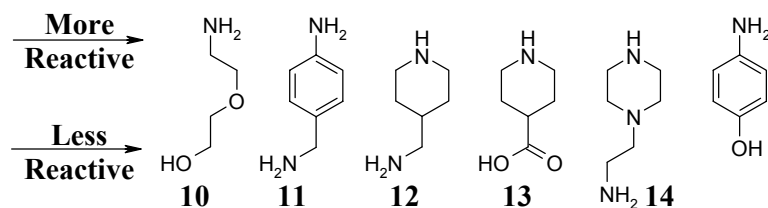
<sup>†</sup> Dioxane used as the solvent

The competition reactions involving *p*-toluidine, **9**, were complicated by the inability to remove the unreacted portion. *p*-Toluidine eluted with the trisubstituted triazine products. Consequently it could not be determined if the chemical shifts of *p*-toluidine originated from its presence in the sample or from substitution on the triazine ring of **1**. Mass spectral analysis of reactions conducted under the same conditions as trials 7 and 8, with amine **7** replacing amine **8**, showed no product with a mass corresponding to substitution of **1** by **9** (Scheme 2.4). It was concluded that *p*-toluidine was not incorporated to any appreciable extent in trials 7 and 8.



**Scheme 2.4.** Competition reaction to determine if *p*-toluidine reacts. The product corresponding to the addition of amine **9** to **1** was not identified by ESI-Mass spectral analysis of the crude reaction.

In selecting heterofunctional linkers for construction of a layered dendrimer the general nucleophilic trend established from the competition reactions was referred to. Several molecules were identified and selected which contained at least two different functional groups showing a large difference in the propensity to substitute monochlorotriazines (Figure 2.2). These linkers have found use as chemoselective building blocks in the convergent syntheses of melamine dendrimers.



**Figure 2.2.** Structures of bifunctional linkers. These linkers contain two functional groups with a marked difference in reactivity with monochlorotriazines. The first five linkers (**10-14**) were used in the construction of a melamine layered dendrimer.

## 2.4 Synthesis of a Layered Dendrimer

### 2.4.1 Target molecule

To demonstrate the utility of chemoselective difunctional linkers in the construction of a dendrimer, a target was identified which contained a unique linking group incorporated at each

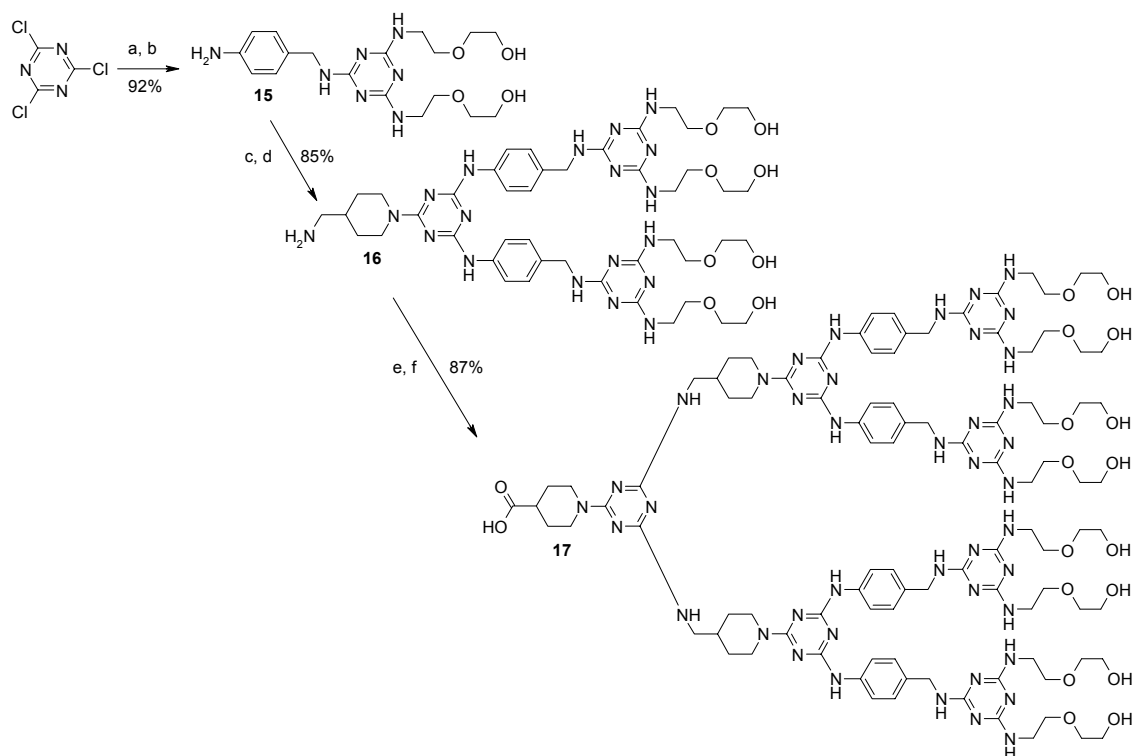
layer of the dendrimer. The target was synthesized in a one-generation per pot approach using chemoselective linkers identified through competition reactions.

#### 2.4.2 Materials and methods

The layered dendrimer synthesis was conducted in such a manner as to produce one generation of growth in a one-pot two step reaction sequence. The reaction sequence is outlined in Scheme 2.5. The primary amine of the surface group, 2-(2-aminoethoxy)ethanol (**10**, AEE), reacts selectively with cyanuric chloride. Addition of two equivalents of AEE resulted in a monochlorotriazine containing two free hydroxyl groups. The alcohols were left unprotected for the entire synthesis, and no competing or substitution reactions between the hydroxyl groups and cyanuric chloride were observed. Completion of the first two substitutions, as monitored by TLC, was followed with addition of the chemoselective linker *p*ABA (**11**). Following completion of the reaction and purification, NMR analysis revealed exclusively the product corresponding to substitution by the benzylic amine. The resulting hydroxyl terminated aromatic amine G1 building block **15** was isolated after purification by silica gel chromatography in 92% yield.

The linker 4-aminomethylpiperidine (**12**, AMP) is as a molecule which capitalizes on the increased nucleophilicity of secondary amines over primary amines. After reaction of **15** with half and equivalent of cyanuric chloride, and completion of the reaction to form the monochlorotriazine as visualized by TLC, AMP was added. The product, **16**, was isolated in 85% yield after silica gel chromatography. NMR analysis showed a product corresponding exclusively to substitution by the secondary amine. This was evident by the large shift in peak frequency of the protons  $\alpha$  to the secondary amine. There was no corresponding change in the chemical shift of the protons  $\alpha$  to the primary amine.

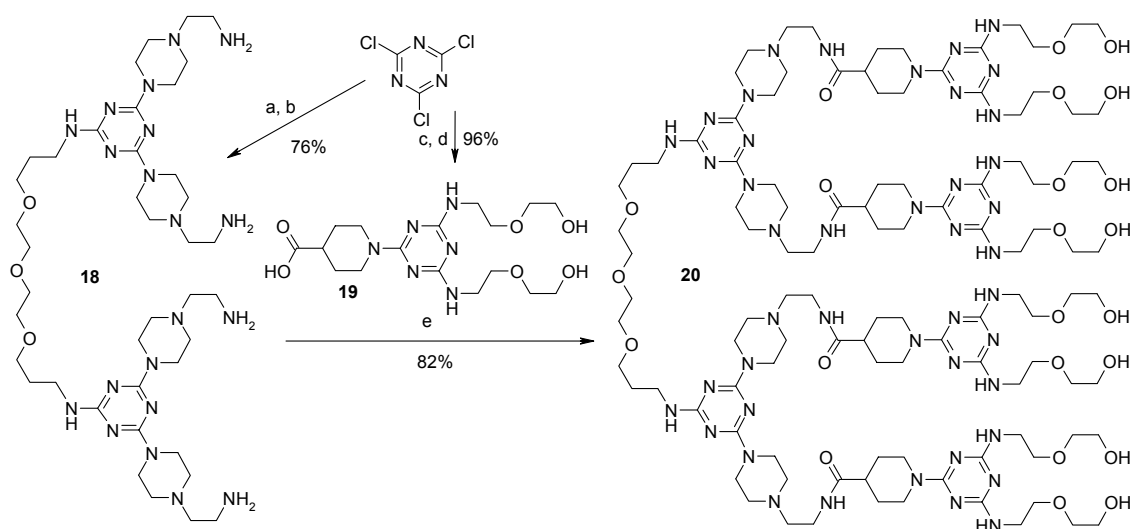
The amino acid isonipecotic acid (**13**, INP) was identified as a bifunctional linker with a reactive secondary amine. The presence of a free carboxylic acid provided further opportunities to modify the resulting dendron through manipulation of the acid at the focal point of the dendron. Substitution by two equivalents of **16** on cyanuric chloride was followed with addition of INP to the reaction. The resulting product, the dendron **17**, was isolated in 87% yield after silica gel chromatography. The resulting G3 dendron with four unique linkage groups was constructed in three steps and 68% overall yield.



**Scheme 2.5.** Dendron synthesis. Reagents and conditions: a) AEE, DIEA, THF, 0 °C→rt, 24 h; b) *p*ABA, 80 °C, 24 h; c) CC, DIEA, THF, 0°C→rt, 24 h; d) AMP, rt, 24 h; e) CC, DIEA, THF-10% MeOH, 0°C→rt, 24 h; (f) INP, NH<sub>4</sub>OH<sub>(aq)</sub>, 50 °C, 24 h. AEE = HO(CH<sub>2</sub>)<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, DIEA = Diisopropylethylamine, *p*ABA = *p*-aminobenzylamine, CC = cyanuric chloride, AMP = 4-aminomethyl piperidine, INP = isonipecotic acid.

To further demonstrate the utility of temperature controlled substitution of cyanuric chloride a tetrafunctional G1 dendrimer, **18**, was synthesized in a single pot (Scheme 2.6, steps a and b). The rationale was to construct an amine terminated core molecule to which four dendrons could be attached, specifically the addition of dendron **17** by way of the free carboxylic acid. This was to be an example of the ‘hypermonomer’ approach. The substitution of the second chloride of cyanuric chloride with primary amines typically occurs in 12-14 hours at room temperature, suggesting the dichlorotriazine is more reactive than the monochlorotriazine. The dichlorotriazine being more reactive is therefore likely to result in less selectivity for substitution by competing amine nucleophiles. To ensure chemoselective substitution of a dichlorotriazine using the heterobifunctional linker 1-(2-aminoethyl)piperazine (**14**, AEP) the temperature for the reaction began at -78 °C and was slowly elevated to room temperature.

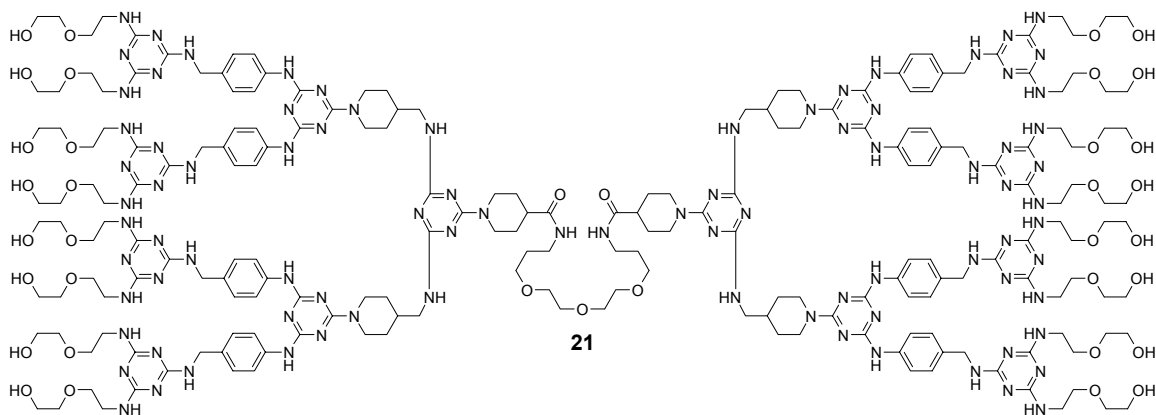
The synthesis of **18** was initiated with reaction of two equivalents of cyanuric chloride with one equivalent of the long chain diamine, 4,7,10-trioxa-1,13-tridecanediamine (TODA) (Scheme 2.6, step a). The reaction was conducted at 0 °C, and within five minutes TLC showed a single product, with no free amines present in the reaction as determined by ninhydrin staining. The reaction was then cooled to -78 °C in a dry ice/isopropanol bath, followed by addition of four equivalents of AEP relative to cyanuric chloride. The reaction stirred for one hour in the dry ice/isopropanol bath followed by slow elevation of the reaction temperature to ambient over 4 hours. The reaction stirred at room temperature for an additional twelve hours. The tetraamine core **18** was isolate in 76% yield using silica gel chromatography. The selective substitution of the secondary amine in the presence of the primary amine is proven by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. A distinct downfield shift of the protons and carbons  $\alpha$  to the secondary amine of AEP is evident. The chemical shift corresponding to the protons  $\alpha$  to the primary of amine of **18** remained the same as those found in the  $^1\text{H}$  NMR of AEP.



**Scheme 2.6.** Dendrimer synthesis. Reagents and conditions: a) 7, 10-trioxa-1, 13 tridecanediamine, DIEA (TODA); THF-10% MeOH, 0 °C, 5 m; b) AEP, -78 °C→rt, 15 h; c) AEE, DIEA, THF-10% MeOH, 0 °C→rt, 8 h; d) INP,  $\text{NH}_4\text{OH}_{(\text{aq})}$ , 60 °C, 12 h. e) PyBOP, DIEA, DMF, 0 °C→rt, 18 h. AEP = 1-(2-aminoethyl)piperazine, PyBOP = Benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate.

To form a dendrimer and demonstrate the selective amine condensation of **18** with a carboxylic acid in the presence of unprotected alcohols the attachment of dendron **17** to the core **18** was attempted under several different coupling conditions. The reactions proved unfruitful, and the attachment of even one dendron **17** to the core could not be proven. To test the viability of the chemistry involved in coupling four dendrons to the core molecule **18** a smaller dendron was used. The G1 analog, **19**, of the G3 dendron was synthesized, proceeding cleanly in a one-pot strategy, giving **19** in 96% isolated yield (Scheme 2.6, steps c and d). Four equivalents of **19** cleanly coupled to the core **18** yielding the G2 dendrimer **20**. The chemistry was viable, but divergent growth of dendrimers is notorious for the introduction of defects due to increased steric crowding as the generation of the dendrimer increases. However, this does not explain the inability of even one G3 dendron **17** to couple to the core **18**.

To further explore the possibility of coupling **17** together to form a dendrimer in the presence of free alcohols the long chain diamine TODA was used with the HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) coupling reagent in a DMF solution. A species present in the MALDI-TOF mass spectrum correspond to the desired product **21**, while the major peak corresponded to a species with the diamine linker attached to only one dendron. A satisfactory separation of the products could not be obtained due to the polarity of the compounds and the limited material available.



## 2.5 Conclusions

The dendrons **15-17** are isolated as fine white powders with limited solubility in organic solvents. Equal mixtures of dichloromethane and methanol or tetrahydrofuran and methanol are most effective at solubilizing the products. The material can also be dissolved in dimethyl formamide (DMF) and readily precipitated from solution using isopropanol. As reactions occur between cyanuric chloride and DMF the synthesis of the dendrimer was conducted in mixed solvent systems. Dendrimer **20** is soluble in methanol and acidic water. The presence of free hydroxyl groups offers the potential for post-synthetic modification of the scaffold, and peracetylation of **17** has been achieved.

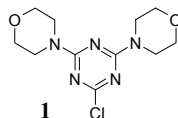
Chemoselective reactivity of triazines in combination with temperature controlled substitution provides rapid access to melamine dendrimers of controlled composition. The synthetic methods described can be applied to the construction of a variety of melamine dendrimers with controlled composition within the dendrimer structure and at the out most layer. Efforts to control the surface functionality are further described in Chapter III.

## 2.6 Experimental: Preparation and Characterization

General: Solvents were reagent grade and used without further purification. Cyanuric chloride, isonipecotic acid, diethylamine, *p*-toluidine, *n*-butylamine, and 1-(2-amioethyl)-piperazine (Acros), DIEA, 2-(2-aminoethoxy)ethanol, *p*-aminobenzylamine, 4,7,10-trioxa-1,13-tridecanediamine, *N*-methylpiperazine, *p*-methylbenzylamine, benzylamine (Aldrich), 4-(aminomethyl)piperidine, 1-acetylpiperazine (TCI), morpholine (Fluka), and piperidine (Advanced ChemTech) were used as received from suppliers without further purification.

NMR spectra were obtained from the use of a Varian Mercury 300 MHz or Inova 500 MHz spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported as  $\delta$  (ppm = parts per million) relative to the residual solvent peak appearing from the deuterated solvent used. Thin-layer chromatography (TLC) was performed using EMD silica gel 60 F<sub>254</sub> pre-coated plates (0.25 mm). Flash chromatography was performed using EMD silica gel 60 (0.040 mm particle size). All compounds were judged pure by TLC analysis (single spot/ two solvent systems) using a UV lamp and/or ninhydrin staining. All mass spectral analyses were carried out by the Laboratory for Biological Mass Spectrometry (LBMS) at Texas A&M.





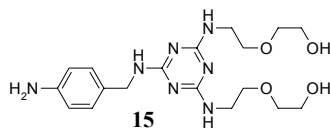
**2-Chloro-4,6-dimorpholino-1,3,5-triazine (1).** To a stirred solution of cyanuric chloride (5.00 g, 27.1 mmol) in THF (250 mL) at 0 °C was added 2 eq. morpholine (4.75 mL, 54.2 mmol) and Hunig's Base (DIEA) (10.4 mL, 59.8 mmol). The reaction stirred for 6 h, followed by filtration to remove salts, and removal of the solvent. The crude product was then dissolved in hot methanol, and precipitated by cooling. The product was recrystallized from methanol again to give a white solid (6.85 g, 88%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 3.68 (br t,  $J = 4.5$  Hz, 8H), 3.60 (t,  $J = 4.5$  Hz, 8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 69.42, 164.17, 66.41, 43.63; MS (ESI): exact mass calcd for  $\text{C}_{11}\text{H}_{16}\text{ClN}_5\text{O}_2 = 285.10$ ; found 286.10  $[\text{M}+\text{H}]^+$ .

**Typical Competition Reaction (Trial 1).** Piperidine **2** (179 mg, 2.10 mmol), *N*-methyl piperazine **3** (210 mg, 2.10 mmol), *N*-acetyl piperazine **4** (269 mg, 2.10 mmol) were added to a Parr vessel with THF (10 mL), (for trial 8, 10 mL Dioxane was used). To this solution **1** (200 mg, 0.700 mmol) was added, and the reaction was left to stir. For those reactions at elevated temperature the solution was brought to ~50 °C before addition of **1**, and then the vessel was sealed. Each reaction was left to stir 18 hours, and TLC confirmed the absence of starting material **1** for all reactions. The solvent was then removed, and the residue was passed through a silica gel column with  $\text{CH}_2\text{Cl}_2$ :MeOH (9:1) to remove excess amines. All fractions containing UV-active compounds that were not positive to ninhydrin staining, (indicating the absence of free amines) were combined and then analyzed by NMR.

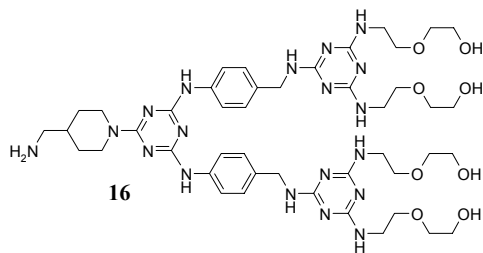
For Trials 7 and 8, unreacted *p*-toluidine could not be separated from the UV-active compounds that were negative to ninhydrin staining, so NMR was taken of the crude mixture. No large shift of protons corresponding to the addition amine **9** to **1** was observed. To rule out the addition of amine **9** to **1** ESI-MS analysis was used on a crude reaction mixture conducted with amines **5**, **7**, and **9** and the monochlorotriazine **1**. While the  $[\text{M}+\text{H}]^+$  for the addition of amine **5** to **1** (exact mass calcd for  $\text{C}_{15}\text{H}_{26}\text{N}_6\text{O}_2 = 322.21$ ; found 323.22  $[\text{M}+\text{H}]^+$ ) and **7** to **1** (exact mass calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_6\text{O}_2 = 370.21$ ; found 371.22  $[\text{M}+\text{H}]^+$ ) were readily observed, no peak corresponding to the addition of amine **9** to **1** was observed (exact mass calcd for

$C_{18}H_{24}N_6O_2 = 356.20$ ; nothing found ). Under these conditions it was inferred that *p*-toluidine does not substitute when in competition with benzylic or aliphatic amines.



**Intermediate 15.** In a Parr vessel 2-(2-aminoethoxy)ethanol (2.20 mL, 21.7 mmol) and DIEA (3.80 mL, 21.9 mmol) were added with 75 mL THF. The mixture was cooled in an ice bath, followed by addition of cyanuric chloride (2.00 g, 10.9 mmol). The reaction was warmed to room temperature and stirred for 24 h. Next *p*-aminobenzylamine (5.00 mL, 43.5 mmol) was added. The vessel was sealed, and heated to 70 °C for 24 h. The salts were filtered off and the solvent was removed. The product was purified by silica gel chromatography with  $CH_2Cl_2$ :MeOH (8:2) with 1% v/v conc.  $NH_4OH$  to give a yellow oil (4.06 g, 92%).

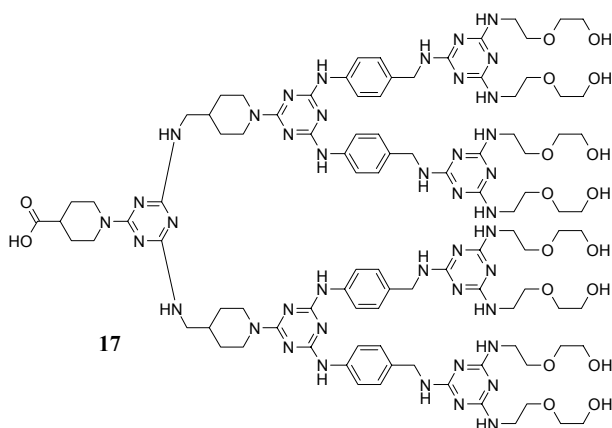
$^1H$  NMR (300 MHz,  $DMSO-d_6$ ,  $\delta$ ): 6.95 (d,  $J = 7.5$  Hz, 2H), 6.48 (d,  $J = 7.5$  Hz, 2H), 4.20 (s, 2H), 3.52 (br, 8H), 3.46 (t,  $J = 4.8$  Hz, 4H), 3.39 (br t, 4H);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ ,  $\delta$ ): 166.23, 147.70, 128.95, 114.36, 72.70, 69.89, 60.79, 43.52;  $^{13}C$  NMR (75 MHz,  $CD_3OD$ ,  $\delta$ ): 165.73, 146.22, 129.67, 128.23, 115.46, 72.33, 69.33, 61.13, 43.82, 40.30; MS (FAB): exact mass calcd for  $C_{18}H_{29}N_7O_4 = 407.23$ ; found 408.23  $[M+H]^+$ .



**Intermediate 16.** Intermediate **15** (3.93 g, 9.64 mmol) was dissolved in 100 mL  $CH_2Cl_2$ :MeOH (1:1) followed by addition of DIEA (1.6 mL, 9.2 mmol) in a Parr vessel. The reaction was cooled in an ice bath and cyanuric chloride (890 mg, 4.84 mmol) was added. The reaction warmed to room temperature and was stirred for 24 h. 4-Aminomethylpiperidine (2.3 mL, 19

mmol) was added to the reaction and stirred at room temperature for 24 h. The solvent was removed and the residue was purified by silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (8:2-7:3) with 1% v/v conc. NH<sub>4</sub>OH to give a white solid (4.11 g, 85%).

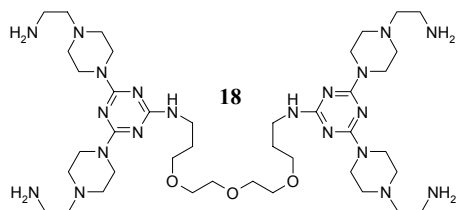
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ): 7.62 (d, 4H), 7.15 (d, 4H), 4.66 (d, 2H), 4.35 (s, 4H), 3.40 (br m, 32H), 2.81 (br, 2H), 2.43 (br d, 2H), 1.74 (br d, 2H), 1.55 (br, 1H), 1.01 (br q, 2H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ): 166.24, 164.88, 164.64, 139.15, 134.62, 128.11, 120.23, 72.65, 69.82, 60.80, 47.33, 43.61, 40.00, 30.07; MS (ESI) exact mass calcd for C<sub>45</sub>H<sub>69</sub>N<sub>19</sub>O<sub>8</sub> = 1003.56; found 1004.57 [M+H]<sup>+</sup>.



**Dendron 17.** Intermediate **16** (300 mg, 0.299 mmol) was dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>:MeOH (1:1) with approx. 0.2 mL of DIEA (~1.2 mmol) in a Parr vessel. The reaction was cooled in an ice bath followed by addition of cyanuric chloride (27.0 mg, .147 mmol). The reaction warmed to room temperature and stirred for 24 h. To the reaction was added isonipecotic acid (77.0 mg, 0.597 mmol) with 1 mL conc. NH<sub>4</sub>OH. The reaction was sealed and heated at 50 °C for 24 h. The solution was allowed to cool and the solvent was removed. The residue was purified by silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (8:2) with 1% v/v conc. NH<sub>4</sub>OH to give a white solid (0.28 g, 87%).

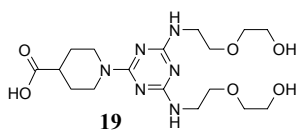
<sup>1</sup>H NMR (500MHz, DMSO-*d*<sub>6</sub>, δ): 7.64 (br, 8H), 7.17 (br, 8H), 4.65 (br, 4), 4.47 (br, 2H), 4.36 (br, 8H), 3.42 (br, 64H), 3.13 (br, 4H), 2.85 (br, 6H), 2.47 (br, 1H), 1.82 (br, 4H), 1.72 (br, 4H), 1.42 (br, 2H), 1.08 (br, 4H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ): 176.52, 166.27, 165.96, 164.78, 164.62, 164.43, 164.35, 138.95, 134.23, 127.68, 119.86, 72.39, 69.54, 60.68,

45.61, 43.17, 42.27, 41.24, 39.92, 36.83, 36.44, 29.96, 28.13; MS (MALDI-TOF) exact mass calcd for  $C_{99}H_{146}N_{42}O_{18}$  = 2211.18; found 2212.73  $[M+H]^+$ , 2234.72  $[M+Na]^+$ .



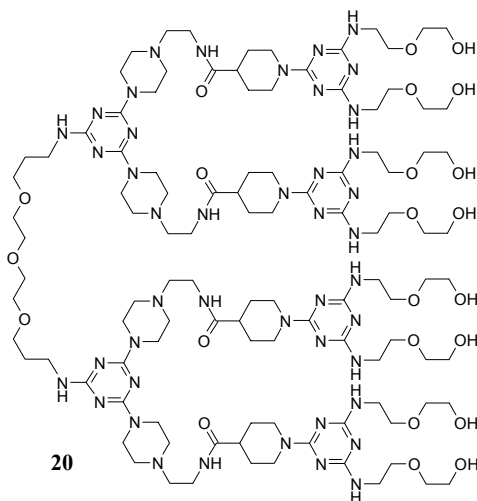
**Tetraamine core 18.** To 90 mL THF with 10 mL MeOH was added 4,7,10-trioxa-1,13-tridecanediamine (598 mg, 2.72 mmol) with DIEA (3.00 mL, 17.3 mmol). The reaction was cooled in an ice bath and cyanuric chloride was added (1.00 g, 5.43 mmol). After 5 min the TLC showed consumption of cyanuric chloride and a single UV active spot with no free amines as detected by ninhydrin staining. The reaction was then cooled in a dry ice/isopropanol bath. 1-(2-aminoethyl)piperazine (4.20 g, 32.6 mmol) was added drop-wise while the solution was cooled. The reaction was left to stir in the ice bath for 1 h, then was slowly allowed to warm to room temperature over 4 h. The reaction was left to stir an addition 12 h, then the salts were filtered off and the solvent removed. The residue was purified by silica gel chromatography with  $CH_2Cl_2$ :MeOH (8:2) with 3% v/v conc.  $NH_4OH$  to give a white solid after drying (2.41 g, 76%).

$^1H$  NMR (500 MHz,  $CDCl_3$ ,  $\delta$ ): 3.61 (br, 16H), 3.52 (m, 4H), 3.47 (m, 4H), 3.42 (t,  $J$  = 6 Hz, 4H), 3.30 (t,  $J$  = 6.5 Hz, 4H), 2.66 (t,  $J$  = 6.5 Hz, 8H), 2.33 (m, 24H), 1.70 (m, 4H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ,  $\delta$ ): 165.95, 164.70, 70.30, 69.92, 69.03, 60.13, 52.90, 42.64, 37.83, 37.71, 37.64, 29.98, 29.33; MS (ESI) exact mass calcd. for  $C_{40}H_{78}N_{20}O_3$  = 886.66; found 887.67  $[M+H]^+$ .



**Intermediate 19.** In a Parr vessel cyanuric chloride (2.00 g, 10.9 mmol) was added to 75 mL THF with 10% MeOH. The mixture was cooled in an ice bath, followed by addition of 2-(2-aminoethoxy)ethanol (2.20 mL, 21.7 mmol) and DIEA (6.0 mL, 34.5 mmol). The reaction was warmed to room temperature and stirred for 8 h. Isonipectic acid (1.4 g, 10.9 mmol) was added to the solution with 5 mL aqueous  $\text{NH}_4\text{OH}$ . The reaction was heated at 60 °C for 12 h. The salts were filtered off and the solvent removed. The crude white solid was washed with water and hot  $\text{CH}_3\text{CN}$  to give a white solid (4.32g, 96%).

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ): 4.58 (br, 2H), 3.67 (m, 4H), 3.60 (m, 4H), 3.55 (m, 8H), 2.98 (br t, 2H), 2.53 (m, 1H), 1.91 (m, 2H), 1.57 (dt, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ): 179.45, 165.34, 73.44, 70.88, 62.23, 43.86, 43.06, 41.44, 29.47;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 176.44, 166.01, 164.65, 72.37, 69.48, 60.47, 42.23, 41.15, 40.00, 28.12; MS (ESI) calcd for  $\text{C}_{17}\text{H}_{30}\text{N}_6\text{O}_6 = 414.22$ ; found 415.33  $[\text{M}+\text{H}]^+$ .



**Dendrimer 20.** Intermediate **19** (350 mg, .845 mmol) was dissolved in DMF (8 mL) and cooled in an ice bath. PyBOP (450 mg, .865 mmol) and DIEA (0.2 mL, 1.2 mmol) were added to the solution, and after mixing this solution was added to core **18** (184 mg, .207 mmol) also in DMF

(5 mL). The solution was removed from the ice bath and stirred for 18 h. The solvent was removed and purified by silica gel chromatography with DCM:MeOH (8:2) and 2% v/v conc.  $\text{NH}_4\text{OH}$ . After drying the product was a white solid (418 mg, 82% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ): 4.74 (br, 8H), 3.75 (br, 16H), 3.66 (m, 16H), 3.62 (m, 4H), 3.58 (m, 20H), 3.53 (m, 36H), 3.39 (t,  $J = 6.5$  Hz, 4H), 3.35 (t,  $J = 6.5$  Hz, 8H), 2.80 (br t, 8H), 2.52 (m, 24H), 2.42 (m, 4H), 1.76 (m, 12H), 1.59 (m, 8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ): 176.62, 166.85, 166.28, 165.61, 165.15, 72.96, 71.12, 70.75, 70.53, 69.82, 61.77, 57.71, 53.56, 44.04, 43.38, 40.90, 38.53, 36.64, 30.17, 29.13; MS (MALDI-TOF) exact mass calcd. for  $\text{C}_{108}\text{H}_{190}\text{N}_{44}\text{O}_{23} = 2471.50$ ; found 2472.74  $[\text{M}+\text{H}]^+$ .

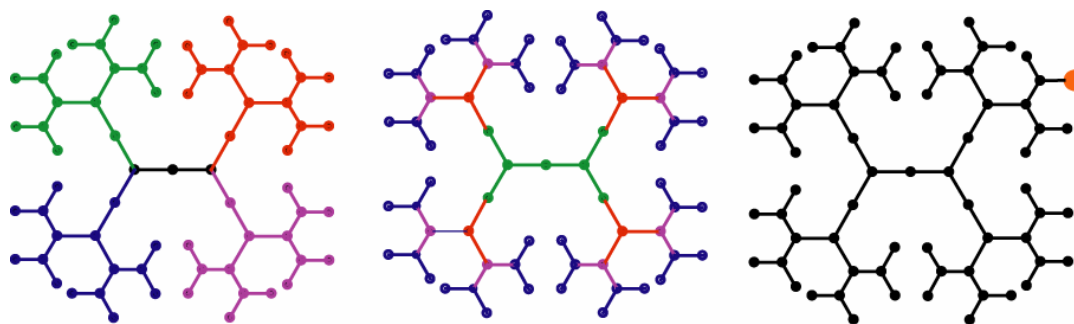
## CHAPTER III

### SYNTHESIS OF A MULTIFUNCTIONAL DENDRIMER CONTAINING ORTHOGONALLY PROTECTED SURFACE GROUPS

#### 3.1 Introduction

Copolymers can be classified by the arrangement of the monomers within the structure, such as alternating, random or block. Dendrimers containing multiple monomers can also be classified into three basic structural classes based on the organization and location of unique structural motifs.<sup>197</sup> In *segmented* dendrimers the unique repeat units are segregated into wedge regions like pieces of a pie, where the slices are of different compositions, and can be compared to block copolymers (Figure 3.1a).<sup>198</sup> The second general class is the *layered* dendrimer, where two or more different repeat units are symmetrically located in a radial fashion giving a layered composition to the dendrimer (Figure 3.1b).<sup>199</sup> Layered-dendrimer can be likened to alternating copolymers and Chapter II describes the synthesis of such a dendrimer.

The final class of dendritic copolymers are the *tailored* dendrimers which have one or more unique groups placed within or at the outermost layer of the dendrimer (Figure 3.1c). Telechelic polymers (polymers with a reactive functional group at one or both ends of the polymer chain) are common in macromolecular chemistry, but by virtue of being linear chain molecules contain a maximum of one or two reactive end groups. Tailored dendrimers are constructed in such a manner as to incorporate a single or multiple unique groups on the periphery of the molecule. The Simanek group has described the syntheses of melamine dendrimers with one or two unique groups out of 16 or 32 surface groups.<sup>170</sup>



**Figure 3.1.** Dendritic copolymers. a) Segmented dendrimer. b) Layered dendrimer. c) Tailored dendrimer.

Dendrimers presenting compositionally diverse surfaces are prepared by two general methods. The first method employs the random multifunctionalization of a dendrimer surface. These dendrimers are not ‘tailored’ in the sense that the exact composition and number of modifications are known, but this method still provides access to macromolecules containing multiple different functionalities. Random functionalizing is achieved by treatment of a dendrimer having reactive surface groups with a substoichiometric amount of a derivatizing reagent. Since a substoichiometric amount of reagent is used, complete derivatization is not accomplished and a percentage of the reactive surface groups remain unmodified. The degree of modification of each molecule can not be controlled, and thus a population of products arises from some dendrimers having more surface groups modified than others. The result is a cocktail of molecules with a statistical distribution of all possible combinations of surface group modifications. Even dendrimers which have the same number of modifications are unlikely to have the same spatial distribution, giving a more complicated mixture of products when structurally isomeric products are considered.

Subsequent reactions can be conducted on dendrimers modified through substoichiometric treatment with a derivatizing agent. The use of a different reagent can be employed to incorporate new groups located at the periphery through modification of another subset of surface groups. Perfunctionalization can also be carried out to modify all the remaining reactive groups. The end result is a population of dendrimers containing multiple different groups at the surface with a statistical and random distribution of the functionality arranged on the dendrimer periphery.<sup>200</sup>

The second method to construct tailored dendrimers focuses on the controlled placement and arrangement of surface functionality by employing a convergent synthetic route, incorporating multifunctional monomers at the dendrimer surface. These truly ‘tailored’ dendrimers contain a single or multiple unique modifications at the periphery of the dendrimer structure.<sup>201</sup> Notably tailored dendrimers have been constructed containing one, two<sup>170,202</sup> or up to eight<sup>203</sup> unique sites at the dendron or dendrimer periphery. However, the ability to post-synthetically and selectively manipulate each unique site in the current examples is limited. A few cases of dendrimers possessing multiple copies of two different types of surface groups which are amenable to separate and selective post-synthetic modifications are present in the literature.<sup>204</sup>



### 3.2 Rationale

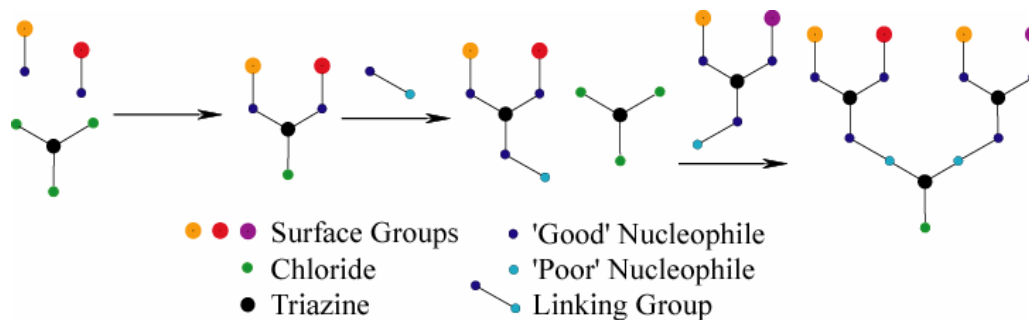
To expand and increase the potential for identification of dendrimer applications, a scaffold which can be post-synthetically and selectively modified is constructed. The ability to selectively modify and tune a dendrimer's surface for a specific application or to incorporate different ligands or multiple molecules of choice for a given experiment greatly expands the utility of the synthetic macromolecule. The dendrimer product moves from just a target molecule, where applications are limited to the composition of the original dendrimer structure, to a flexible scaffold for the attachment of molecules and selective modifications of the periphery as new applications or experiments are devised.

Nature uses a limited number of building blocks to construct functional materials. Rubber starch, cellulose and glycogen are composed of a single type of monomer. DNA is composed of four different monomers. Proteins can be composed of up to 20 different monomers, providing access a wide array of architectural and compositional space. Natural polymers are extensively modified post-synthetically, including the methylation of DNA and the phosphorylation or glycosylation of proteins. Post-synthetic modification of RNA provides a variety of unique architectures with various functions, including tRNAs and rRNAs utilized in protein synthesis. Nature tunes, regulates, and controls the function of biopolymers through post-synthetic modifications.

Polymer chemists typically employ a small number of monomers in the construction of dendrimers and polymers, much like nature in the synthesis of DNA, oligosaccharides, and rubber. Dendrimers syntheses, while providing means to control the composition of macromolecules and define the exact atomic connectivity, typically rely on the iterative addition of a limited number of building blocks. The rapid and efficient incorporation of multiple monomers into dendrimers is desirable to access functional materials and unique architectures, in a similar manner as that utilized by nature to construct proteins.

Representative of methods currently used to construct tailored dendrimers is the route employed by Fréchet in the synthesis of the first truly tailored dendrimer containing one, two or three unique sites at the dendrimer periphery. The dendrimer was synthesized through a convergent route, and relied throughout the synthesis on the monoderivatization of a homobifunctional monomer. The desired singly modified product was fished out of the reaction from the unfunctionalized and difunctionalized products. This route is not atom economical: material is lost at each step either as the unfunctionalized or difunctionalized products.

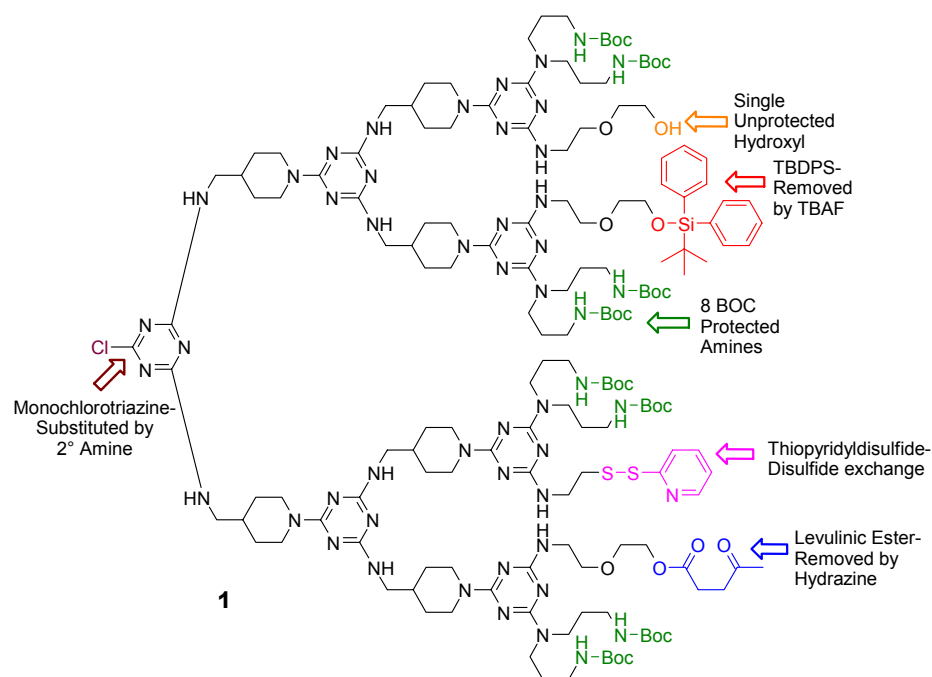
A method to control and ensure the incorporation of a single functionality on a dendrimer monomer during a synthetic route would be advantageous. Temperature controlled substitution of cyanuric chloride using one equivalent of the desired surface group can be followed in the same pot by the addition of a second and different surface group. A third group can subsequently be substituted on the monochlorotriazine ring (Scheme 3.1). The method is efficient and atom economical, as purification is not needed between each reaction, thus shortening the time required to construct dendrimer. By matching the stoichiometry of reagents, the only byproducts are HCl and the base necessary to scavenge it.



**Scheme 3.1.** Schematic outline of steps for construction of a multifunctional dendrimer. Two different surface groups are installed in a stepwise manner on the triazine core (step 1), followed by installation of the linker (step 2). The result is a monomer containing two unique surface groups and a linker for further elaboration of the dendrimer. A second dendron, containing the same or unique surface functionality can be incorporated into the dendrimer at this stage (step 3).

To demonstrate methods by which multiple functionality can be incorporated into melamine a dendrimer and to further illustrate the ease and efficiency by which such routes can be accomplished, a G3 dendrimer was synthesized that not only possesses a compositional diverse surface, but terminal groups bearing multiple functionality by the way of orthogonal protecting and functional groups. The inspiration for such a project stemmed from work which introduced four different orthogonal protecting groups around a sugar nucleus, the most notable of these being Wong's effort in 1998.<sup>205</sup> The G3 dendron possesses two orthogonal electrophilic groups, and three orthogonal nucleophile protecting groups. The surface of the G3 dendron (**1**) contains eight BOC-protected amines, a silyl protected alcohol, a levulinyl ester, a single free

hydroxyl, and a thiopyridyl disulfide, with a monochlorotriazine located at the focal point of the dendron.

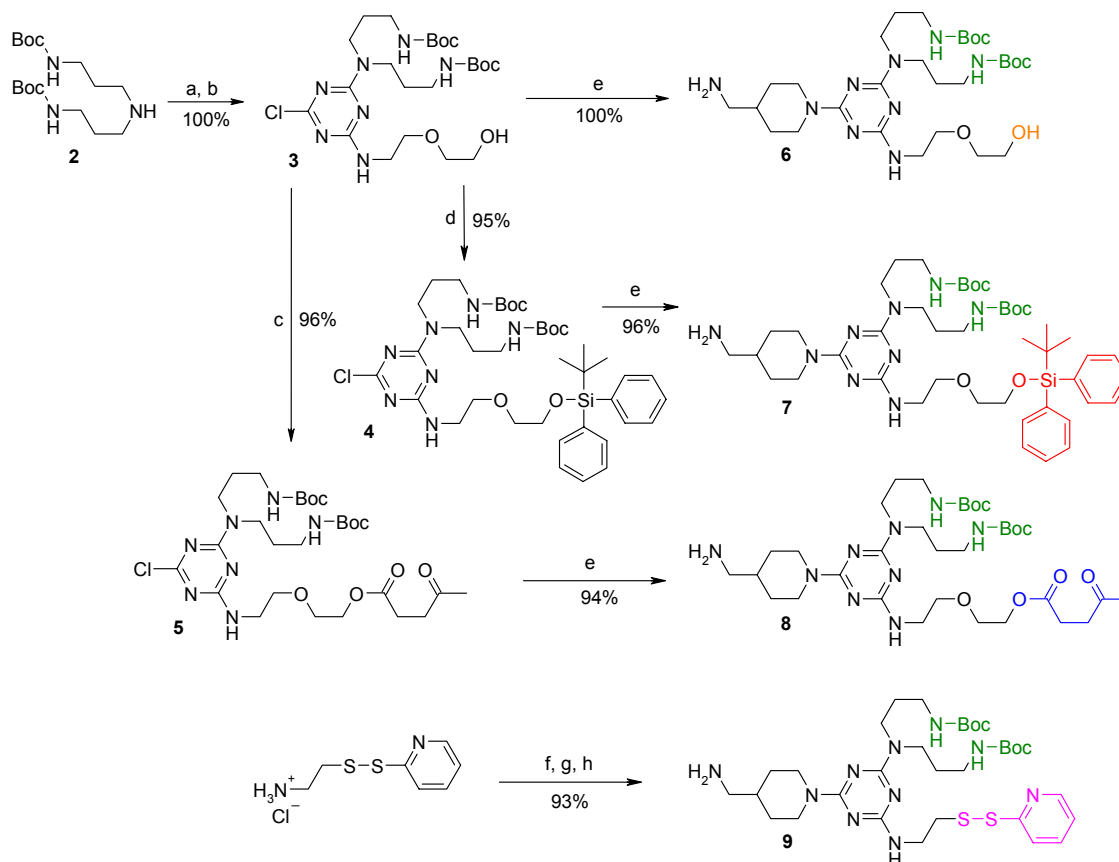


### 3.3 Materials and Methods

The synthesis of **1** was carried out using a highly convergent method where three out of the four surface group building blocks originated from a common intermediate. The reactions were efficient providing typical yields in the mid-nineties. Multiple-functionality is incorporated in a single-pot taking advantage of temperature selective substitution of the triazine core, and the use of bifunctional linking groups which react chemoselective with chlorotriazines. The initial stage for the synthesis of **1** resulted in the completion of the four building blocks which would eventually make up the periphery of the dendrimer. Three of these four dendrons originated from a common precursor as outlined in Scheme 3.2.

The synthesis began with the selective BOC protection of the primary amines of 3,3'-diaminodipropylamine with BOC-ON (2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile),<sup>206</sup> giving the bisprotected triamine **2**. This AB2 type monomer would

compose one-half of the dendrimer periphery. The protected triamine **2** was reacted with one equivalent of cyanuric chloride while the reaction stirred at 0 °C. Upon completion of the first substitution of cyanuric chloride as visualized by thin layer chromatography (TLC) the second surface group was installed in the same pot. Addition of the amino-alcohol (2-aminoethoxy)ethanol at room temperature, followed by work-up and purification give intermediate **3** (Free-OH-Cl) in quantitative yield.

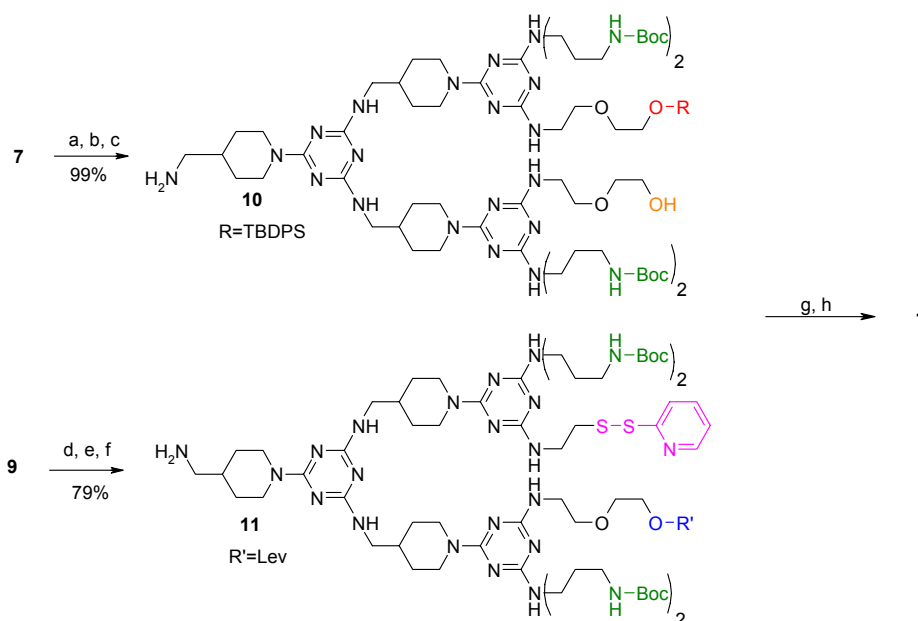


**Scheme 3.2.** Building block syntheses. Reagents and conditions. a) CC, DIEA, THF, 0 °C, 1 h; b) 2-(2-aminoethoxy)ethanol, rt, 18 h; c) Levulinic acid, DCC, DMAP, THF, rt, 8 h; d) TBDPSCl, imidazole, THF, rt, 8 h; e) AMP, THF, rt, 8 h; f) CC, DIEA, THF, 0 °C, 2 h; g) **2**, rt, 24 h. h) AMP, rt, 8 h. CC = cyanuric chloride, DIEA = Diisopropylethylamine, TBDPSCl = tert-Butyldiphenylsilyl chloride, DCC = Dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, AMP = 4-aminomethyl piperidine.

The monochlorotriazine **3** was divided in triplicate for further elaboration to intermediates **6-8**. Intermediate **6** (Free-OH-AMP) was readily synthesized by the selective substitution of the chloride of **3** by the secondary amine of 4-aminomethylpiperidine (AMP). Intermediate **3** was subjected to silylation with TBDPSCl (*tert*-butyldiphenylsilyl chloride). After purification and characterization of intermediate **4** (TBDPS-Cl) addition of AMP afforded intermediate **7** (TBDPS-AMP). Esterification of **3** using the DCC mediated reaction with levulinic acid gave **5** (Lev-Cl), which was subsequently reacted with AMP to give **8** (Lev-AMP).

Three different substitutions of cyanuric chloride were conducted sequentially in a single pot to synthesize fragment **10** (Pyr-AMP). The synthesis commenced with the addition of the HCl salt of thiopyridylcysteine amine<sup>178</sup> to a solution containing cyanuric chloride at 0 °C. The reaction progress was monitored using TLC, and upon completion of the first substitution the bis-BOC-protected triamine **2** was added to the solution stirred at room temperature. Completion of the second substitution was followed with addition of AMP in the same pot. Workup and purification proceeded cleanly, isolating the product **10** in 93% yield.

With the dendrons **6-9** in hand, the second stage involving the syntheses of higher generation dendrons was undertaken. Controlling the stoichiometry of the dendron and the temperature of the reaction were imperative for the synthesis of dendrons **10** and **11** (Scheme 3.3). The syntheses were again carried out in a single pot obviating the need for purification of the monochlorotriazine intermediate. Synthesis of dendron **11** illustrates the effectiveness of monitoring the reaction using TLC. Triazine compounds are UV-active on TLC plates impregnated with the F<sub>254</sub> fluorophore. One equivalent of intermediate **7** (which has an R<sub>f</sub> = 0.3 in 9:1 DCM:MeOH) was mixed with cyanuric chloride at 0 °C. Completion of the first substitution was evident after appearance of a single new spot corresponding to the putative dichlorotriazine intermediate (R<sub>f</sub> = 0.6 in 9:1 DCM:MeOH). Subsequent addition of one equivalent of **6** to the solution at room temperature resulted over time in a single new spot (R<sub>f</sub> = 0.4 in 9:1 DCM:MeOH), the monochlorotriazine. (This intermediate was isolated and characterized from a separate reaction sequence. See Chapter V). The final substitution was accomplished after addition of AMP to the same pot at room temperature. The G2 dendron, with a free primary amine, appeared on the TLC with an R<sub>f</sub> = 0.25. Its purification was easily accomplished using silica gel chromatography in near quantitative yield.



**Scheme 3.3.** Dendron syntheses. Reagents and conditions. a) CC, DIEA, THF, 0 °C, 2 h; b) **6**, rt, 24 h; c) AMP, rt, 18 h; e) CC, DIEA, THF, 0 °C, 2 h; e) **8**, rt, 18 h; f) AMP, rt, 18 h; g) **10**, CC, DIEA, THF, 0 °C, 2 h; h) **11**, rt, 18 h.

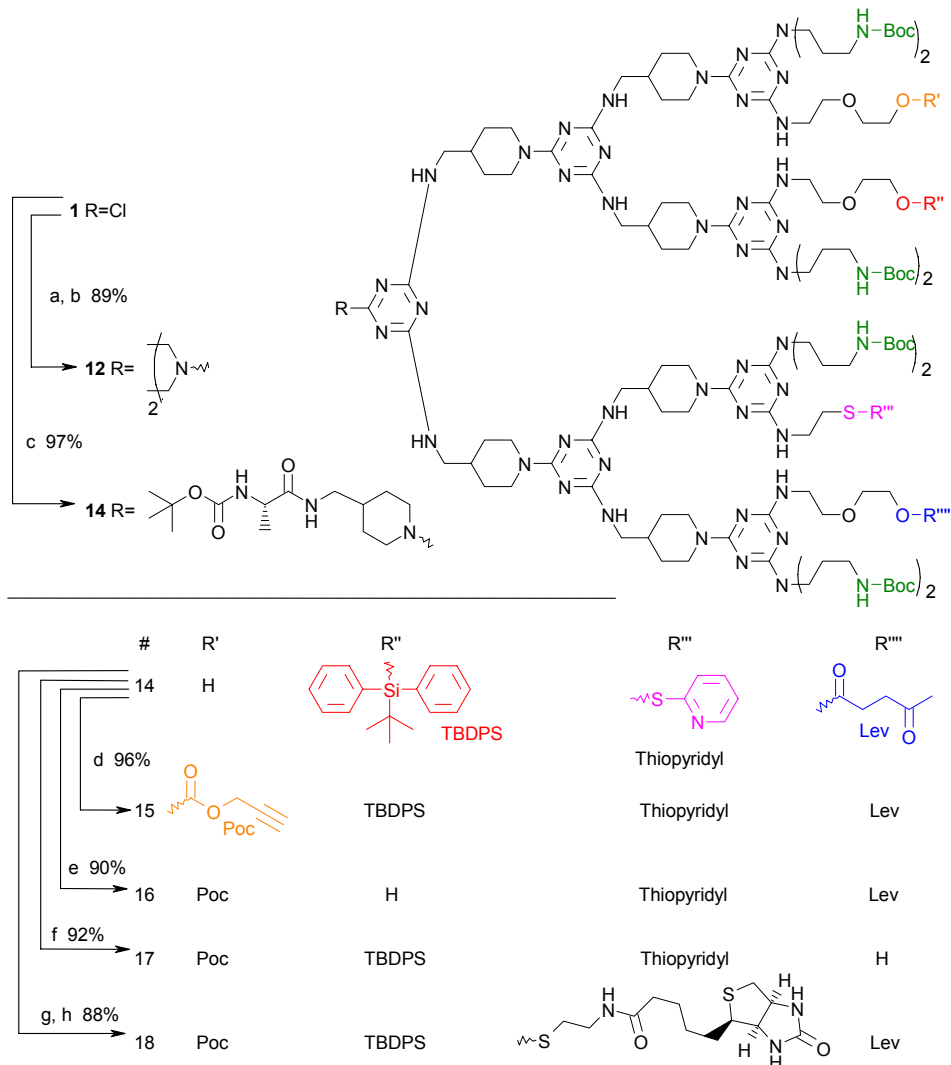
The dendron containing the levulinyl ester and pyridyldisulfide, intermediate **11**, was constructed in a like manner to the synthesis of **10**. A reaction of cyanuric chloride using intermediate **9** was conducted at 0 °C. Mixtures of cyanuric chloride and the levulinyl ester containing intermediate **8** resulted in an almost instantaneous yellow solution and degradation of the starting material, even when the solutions were cooled before mixing. In subsequent reactions the fragment containing the levulinyl ester was never mixed with cyanuric chloride. Completion of the first substitution of cyanuric chloride using intermediate **9** was followed by addition of **8** to the solution. Subsequent reaction with AMP afforded dendron **11**. The product **11** was isolated in only 79% yield, the lowest by 14% for the entire synthetic sequence. While TLC of the completed reaction revealed a single spot, upon work-up and silica gel chromatography several products could be isolated. Upon standing NMR samples degraded, resulting in complicated spectra. Mass spectral analysis revealed peaks corresponding to a mass twice that of the desired product, minus 18 or 32. It was assumed from these results that condensation between the free primary amine of the dendron and the ketone of the levulinyl ester was occurring, giving rise to the observed by-products and resulting in the corresponding lower

and uncharacteristic yield. Indeed  $^1\text{H}$  NMR analysis of a sample presumed to contain **11** gave a convoluted spectrum, but after incubation with a small amount of aqueous HCl yielded an NMR spectrum consistent with that of compound **11**.

The G3 dendron **1** was constructed by the typical route, first reaction of intermediate **10** with one equivalent of cyanuric chloride followed by substitution using one equivalent of intermediate **11**. Dendron **1** was isolated after silica gel chromatography in 95% yield. The synthesis of **1** proceeded in a convergent route with typical yields in the high nineties. The reactions were conducted on a multi-gram scale producing 10.5 grams and ~5 grams of **1** in separate reaction sequences utilizing 18 reactions in 8 convergent steps. The overall yield was ~70% when the lowest yielding step is included. (The longest linear sequence starting with intermediate **2** provides an 80% overall yield).

Dendrimers can be constructed from the multifunctional dendron **1** by dimerization with an appropriate linking molecule using the reactive monochlorotriazine. Piperazine was used to construct the full G3 dendrimer **12** (Scheme 3.4). Due to the large differences in molecular weights between **1** and piperazine (3140.88 Da to 86.14 Da respectively) it would be difficult to ensure the correct stoichiometry of the two reagents. A two-step route was devised to dimerize dendrons of nearly equal molecular mass. Reaction of dendron **1** with excess piperazine resulted in substitution of the monochlorotriazine and the incorporation of a free secondary amine. The excess piperazine was removed by extraction and size exclusion chromatography. The G3 dendron product with a free secondary amine was then reacted with one equivalent of the monochlorotriazine dendron **1** (Scheme 3.4 steps a and b). The reaction was slow, but did result in a G3 dendrimer with a molecular weight of 6,855 Da, containing duplicates of each unique functional group at periphery.

The G3 dendron **1** was used to demonstrate the orthogonal deprotection and modification of the molecule. The monochlorotriazine located at the focal point of the dendron provides a site for attachment of molecules of interest to the scaffold. One such molecule could be a protein transduction domain (PTD) peptide to investigate the translocation of dendrimers across cellular membranes (for further efforts in this area see Chapter V). To demonstrate the feasibility of attaching molecules of interest to the focal point a single amino-acid was linked to the AMP group and subsequently attached to the core of dendron **1** giving dendron **14**.<sup>207</sup>

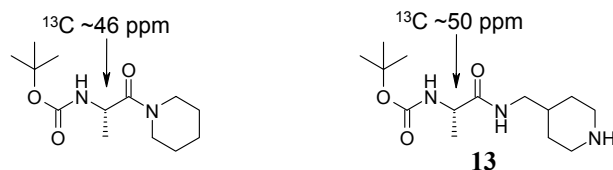


**Scheme 3.4.** Dendrimer synthesis and dendron derivatization. Reagents and conditions. a) piperazine, THF, rt, 20 h; b) **1**, DIEA, MeOH, 10 d; c) BOC-Ala-AMP (**13**), DIEA, THF, rt, 2 d; d) **14**, propargylchloroformate, pyridine, THF, rt, 2 h; e) **15**, TBAF, THF, rt, 4 h; f) **15**, hydrazine, THF, rt, 2 h; g) **15**, DTT, DCM, rt, 2 h; h) Biotin-PCA, DMF, rt, 2 h. BOC-Ala-AMP-**13**-see experimental for preparation. TBAF = tetrabutylammonium fluoride, DTT = dithiothreitol, Biotin-PCA =

The modified amino acid was constructed using AMP and the NHS ester of BOC-alanine. To prove that amide formation arose from the selective reaction with the primary amine of AMP, the piperidine analog was separately constructed.  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis of the two compounds revealed a clear difference in the chemical shift corresponding to the  $\alpha$ -carbon, suggesting the reaction was selective for substitution by the primary amine over the secondary



amine (Figure 3.2). Acylation of **13** revealed a change in the chemical shift of the four protons  $\alpha$  to the secondary amine.



**Figure 3.2.** Chemical shift assignments of the  $\alpha$  carbons of the piperidine and AMP amides of BOC-alanine. Spectra were obtained in, and referenced to  $\text{CDCl}_3$ .

The attachment of the amino acid analog **13** to dendron **1** gave dendron **14** (Scheme 3.4 step c). The reaction was rapid, attesting to the correct assignment of the free secondary amine, as primary amines react slowly with monochlorotriazines. Dendron **14** was used to demonstrate the selective and independent modification of each surface group in the presence of the others through removal of each protecting group individually (Scheme 3.4).

Selective modification or removal of protecting groups can be achieved at the surface of the dendron. To show the selective modification of surface groups, an alkyne was added to the free alcohol forming the propargyl carbonate **15**. Alkynes can be used as sites for click chemistry.<sup>208</sup> Propargyl carbonates (POC) have also found use as protecting groups for amines, alcohols, and carboxylates,<sup>209</sup> and the introduction of POC at the surface represents the incorporation of another orthogonal protecting group. Indeed it was found the POC group was removed during treatment of the dendron with TCEP (Tris(2-carboxyethyl)phosphine hydrochloride) in efforts to modify the thiopyridyl site.

Previous methods for the removal of the POC group from hydroxyls require the use of a heterogeneous solution of tetrathiomolybdate.<sup>209c</sup> The use of TCEP or other phosphines to remove the POC group is an attractive alternative, however the generality of this method is unknown. The POC group is spectrally simple, atom economical as a protecting group, and readily introduced through the use of propargyl chloroformate. The disulfide was reduced as expected under treatment with TCEP and the TBDPS ether and levulinyl ester remained untouched during the reaction. The final reason to incorporate the POC on the free hydroxyls

was to discriminate between the free hydroxyl and the hydroxyls revealed from subsequent removal of the TBDPS and levulinyl protecting groups.

The removal of the TBPDS ether was readily accomplished in the presence of the other functionality with the use of TBAF (tetrabutylammonium fluoride) to give **16**, and no problems were encountered with its use. The removal of the levulinyl ester proceeds cleanly with the use of hydrazine, giving **17**, with no modification of the thiopyridyl disulfide or TBDPS ether. In one case where a large excess of hydrazine was used under concentrated conditions, loss of the POC group was evident by mass spectrometry. This problem was readily remedied through the slow addition of a dilute solution of hydrazine.

Reduction of the disulfide using TCEP resulted in the loss of the POC group, so another route was employed to demonstrate the selective modification at the thiopyridyl disulfide site. The disulfide was reduced using an excess of dithiothreitol (DTT), followed with removal of the excess DTT using size exclusion chromatography. The dendron possessing the free thiol was immediately reacted as the compound eluted from the column with biotin containing an activated disulfide.<sup>210</sup> Dendron **18**, a G3 dendron with a pendant biotin, was isolated in good yield and high purity.

### 3.4 Outlook

The capability of attaching a small molecule of biological significance, such as biotin, opens the door for the use of this scaffold in a number of different investigations. A smaller generation, but similar dendron to molecule **1**, is used in the assembly of novel macromolecular constructs. The preliminary results of which are described in Chapter V.

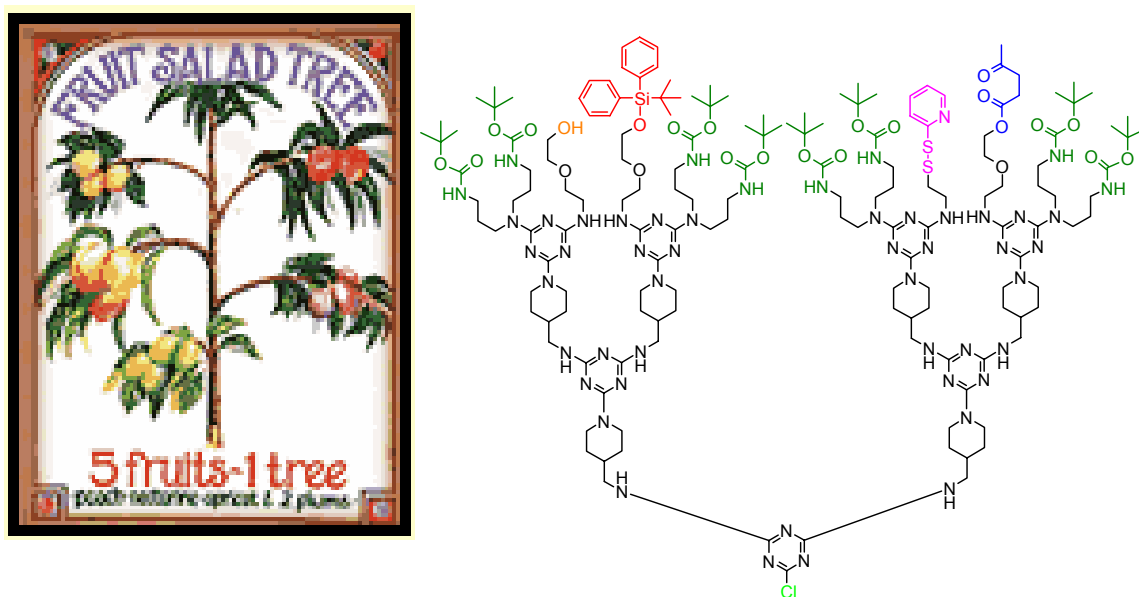
The substitution of piperazine for the chloride on **1** provides a reactive secondary amine handle that has been used for the attachment of the dendron to a trityl-polystyrene resin. The eventual goal is to modify all of the peripheral groups while the scaffold is attached to a solid support. The attachment of multiple different strands of DNA to the scaffold would offer potential uses for this scaffold in the construction of novel hybrid DNA-dendrimer assemblies, the realization of which has only occurred in the imagination.

### 3.5 Conclusions

It is readily apparent that modification of the dendrimer and production of potentially applicable material would be greatly excelled if purification of the intermediates was not

required. The proof-of-concept reactions described provide the basic reaction conditions and understanding of the relevant chemistry necessary for the successful modification of the dendrimer supported on the solid phase. The monochlorotriazine provides a selective handle by which the scaffold may be attached to a solid support. The selective deprotection and efficient modification of the peripheral functionality of the dendron was demonstrated.

Access to highly functionalized dendritic materials on a moderate scale is tractable, and the surface groups are amenable to post-synthetic modification. In keeping with the theme of dendrimers as architecturally analogous to trees, the efforts described here have affectionately become known as the ‘fruit salad tree’ project. Fruit trees can be obtained wherein multiple different types of fruit have been grafted onto a single trunk (Figure 3.3).<sup>211</sup> These single orchard or ‘fruit salad’ trees offer multiple varieties of fruit which ripen in a staggered fashion throughout the growing season. The molecular fruit salad tree has been planted as an example of the ability to tune and control the composition of large molecules. While some fruits have been plucked from and grafted onto the molecular fruit salad tree the autumnal season of its existence is yet to arrive.

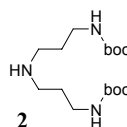


**Figure 3.3.** A drawing of a fruit salad tree and the atomic representation of the molecular fruit salad tree. (Picture used with permission from the Fruit Salad Tree Company found at [www.fruitsaladtree.com](http://www.fruitsaladtree.com).)

### 3.6 Experimental: Preparation and Characterization

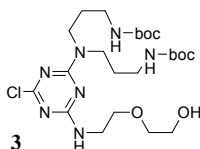
Chemicals were used as received from general chemical suppliers (Aldrich and Acros) without further purification. ACS grade THF and DCM were stored over 4Å sieves and other solvents were used as received.

NMR spectra were obtained from the use of a Varian Mercury 300 MHz or Inova 500 MHz spectrophotometer as indicated.  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are reported as  $\delta$  (ppm = parts per million) relative to the residual solvent peak appearing from the deuterated solvent used. Thin-layer chromatography (TLC) was performed using EMD silica gel 60 F<sub>254</sub> pre-coated plates (0.25 mm). Flash chromatography was performed using EMD silica gel 60 (0.040 mm particle size). All compounds were judged pure by TLC analysis (single spot/ two solvent systems) using a UV lamp and/or ninhydrin staining. All mass spectral analyses were carried out by the Laboratory for Biological Mass Spectrometry (LBMS) at Texas A&M.



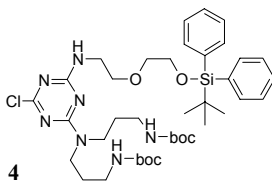
**Intermediate 2.** (BisBOCTriamine). A solution of 3,3'-diaminodipropylamine (8.5 mL, 60.9 mmol) and Hunig's base (DIEA, diisopropylethylamine) (30 mL, 172 mmol) in 50 mL THF was added to an ice-bath cooled solution of BOC-ON (2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile) (30.0 g, 122 mmol) in 250 mL of THF. The reaction warmed to room temperature over 4 h, and the solvent was then removed by reduced-pressure evaporation. The residue was dissolved in 250 mL of DCM and washed with 2 portions of 200 mL H<sub>2</sub>O, followed by washing with 200 mL of brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed by reduced-pressure evaporation to give a thick oil. A small portion of MeOH was added to the oil, followed by the addition of 200 mL of EtOAc. After storage of the solution overnight at 0 °C the product was isolated by filtration to give a white solid (16.4 g, 81%).

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$ ): 3.16 (br m, 4H), 2.61 (t,  $J$  = 6.3Hz, 4H), 1.61 (m, 4H), 1.39 (s, 18H);  $^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>,  $\delta$ ): 155.95, 78.89, 47.28, 38.80, 29.64, 28.43; MS (ESI) exact mass calcd for C<sub>16</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub> = 331.25; found 332.24 [M+H]<sup>+</sup>.



**Intermediate 3.** (Free OH-Cl). Intermediate **2** (10.0 g, 30.2 mmol) was dissolved in 150 mL THF, followed by addition of DIEA (16.0 mL, 91.9 mmol). The solution was cooled in a salt/ice-bath. Cyanuric chloride (5.56 g, 30.2 mmol) was added to the solution and stirred while cooled for 1 h. 2-(2-aminoethoxy)ethanol (6 mL, 60.0 mmol) was added to the reaction followed by the addition of 25 mL MeOH. The reaction was stirred for 18 h, followed by removal of the salts from solution by filtration, and solvent removal by reduced-pressure evaporation. The residue was dissolved in 200 mL DCM, and washed with 200 mL H<sub>2</sub>O followed by washing with 200 mL of brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, followed by removal of the solvent by reduced-pressure evaporation. The product was further purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant. The product was isolated as a white hygroscopic solid (16.6g, 100%).

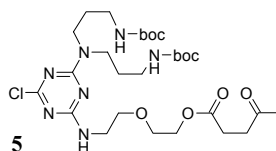
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ ): 3.76 (m, 2H), 3.56 (m, 2H), 3.49 (m, 2H), 3.43 (m, 8H), 2.92 (m, 4H), 1.63 (m, 2H), 1.58 (m, 2H), 1.29 (br, 18H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>,  $\delta$ ): 168.10, 164.72, 164.51, 156.41, 156.20, 79.14, 78.90, 72.15, 72.06, 69.45, 68.89, 61.12, 61.00, 44.02, 43.83, 43.53, 40.56, 40.44, 37.59, 37.42, 37.70, 28.03, 27.41; MS (APCI) exact mass calcd for C<sub>23</sub>H<sub>42</sub>ClN<sub>7</sub>O<sub>6</sub> = 547.3; found 548.1 [M+H]<sup>+</sup>.



**Intermediate 4.** (TBDPS-Cl). Intermediate **2** (4.0 g, 7.3 mmol) was dissolved in 50 mL of dry THF, followed by addition of *tert*-butyldiphenylchlorosilane (TBDPS-Cl) (2.2 mL, 8.4 mmol),

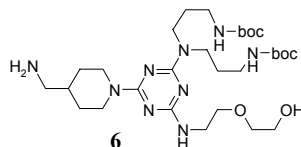
imidazole (400 mg, 5.9 mmol) and DIEA (1.5 mL, 8.6 mmol). The reaction stirred for 8 h, followed by removal of the solvent by reduced-pressure evaporation, to give a white foam. The product was purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant to give a white solid (5.5 g, 95%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.57 (m, 4H), 7.29 (m, 6H), 3.69 (m, 2H), 3.48 (m, 12H), 2.97 (m, 4H), 1.62 (m, 4H), 1.34 (s, 9H), 1.32 (s, 9H), 0.94 (s, 9H);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 168.37, 164.93, 164.69, 156.47, 156.20, 135.35, 133.27, 129.53, 127.50, 79.25, 79.02, 72.20, 72.02, 69.60, 69.25, 63.17, 43.92, 43.52, 40.61, 37.36, 36.74, 28.15, 27.42, 26.55, 18.94; MS (ESI) exact mass calcd for  $\text{C}_{39}\text{H}_{60}\text{ClN}_7\text{O}_6\text{Si}$  = 785.40; found 786.43  $[\text{M}+\text{H}]^+$ .



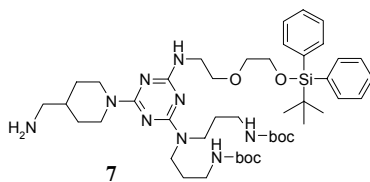
**Intermediate 5.** (Lev-Cl). Intermediate **2** (5.0 g, 9.1 mmol) was dissolved in 50 mL dry THF. Levulinic acid (2.0g, 17.2 mmol), DCC (4.0 g, 19.4 mmol), and DMAP (500 mg, 4.1 mmol) were added to the flask and left to stir for 8 h. The solids were filtered off, and the solvent removed by reduced-pressure evaporation. The product was purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant to give a colorless oil (5.7 g, 96%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 4.22 (m, 2H), 3.66 (m, 2H), 3.62 (m, 4H), 3.58 (m, 4H), 3.08 (m, 4H), 2.78 (t,  $J$  = 6.47 Hz, 2H), 2.61 (t,  $J$  = 6.47 Hz, 2H), 2.20 (s, 3H), 1.77 (m, 2H), 1.72 (m, 2H), 1.44 (s, 18H);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.76, 172.76, 168.69, 165.30, 165.05, 156.12, 155.84, 79.17, 78.81, 69.74, 69.16, 68.97, 68.78, 43.76, 43.99, 40.67, 37.85, 37.47, 36.76, 29.82, 28.38, 27.67; MS (ESI) exact mass calcd for  $\text{C}_{28}\text{H}_{48}\text{ClN}_7\text{O}_8$  = 645.32; found 646.35  $[\text{M}+\text{H}]^+$ .



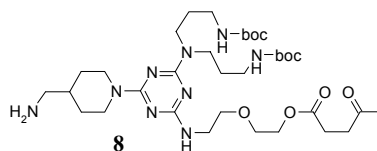
**Intermediate 6.** (Free OH-AMP). Intermediate **2** (5.0 g, 9.1 mmol) was dissolved in 50 mL of THF followed by the addition of 4-aminomethyl piperidine (AMP) (3.3 mL, 27.4 mmol). The reaction stirred for 8 h at room temperature. The solids were filtered off and washed with THF. The solvent was then removed by reduced-pressure evaporation and the residue was purified by silica gel chromatography using 9:1-8:2 DCM:MeOH with 1% NH<sub>4</sub>OH as the eluant, to give a white hygroscopic solid (5.7 g, 100%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ): 4.56 (br, 2H), 3.71 (br, 4H), 3.57 (br t, 2H), 3.49 (br t, 2H), 3.45 (m, 10H), 2.92 (br s, 4H), 2.66 (t, *J* = 12.5 Hz, 2H), 2.43 (d, *J* = 7.0 Hz, 2H), 1.61 (br m, 6H), 1.44 (m, 1H), 1.30 (s, 18H), 0.98 (dq, *J* = 12.5, 3.5 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ): 166.08, 165.54, 164.64, 156.57, 79.38, 72.46, 70.04, 61.46, 47.54, 43.37, 42.70, 40.51, 39.49, 37.31, 29.75, 28.48, 27.78; MS (APCI) exact mass calcd for C<sub>29</sub>H<sub>55</sub>N<sub>9</sub>O<sub>6</sub> = 625.4; found 626.3 [M+H]<sup>+</sup>.



**Intermediate 7.** (TBDPS-AMP). Intermediate **4** (5.0 g, 6.4 mmol) was dissolved in 50 mL THF followed by addition of AMP (2.3 mL, 19.1 mmol). The reaction was stirred for 8 h at room temperature, after which the salts were filtered off and washed with THF. The solvent was removed by reduced-pressure evaporation and the product was purified by silica gel chromatography using 9:1 DCM:MeOH with 1% NH<sub>4</sub>OH as the eluant, to give a white solid (5.3 g, 96%).

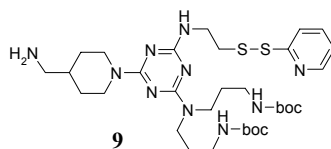
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.59 (m, 4H), 7.29 (m, 6H), 4.64 (br s, 2H), 3.71 (t,  $J = 5.5$  Hz, 2H), 3.50 (m, 10H), 3.39 (br s, 4H), 2.95 (s, 4H), 2.69 (t,  $J = 12.5$  Hz, 2H), 2.47 (d,  $J = 6.5$  Hz, 2H), 1.64 (m, 6H), 1.47 (m, 1H), 1.34 (s, 18H), 1.02 (dq,  $J = 12.5, 3.5$  Hz, 2H), 0.96 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 165.69, 165.25, 164.35, 156.03, 135.26, 133.26, 129.34, 127.36, 78.79, 71.93, 69.83, 63.08, 47.23, 42.91, 42.05, 41.80, 40.31, 40.20, 39.13, 36.86, 36.69, 36.59, 29.37, 28.12, 27.37, 27.21, 26.47, 18.84; MS (ESI) exact mass calcd for  $\text{C}_{45}\text{H}_{73}\text{N}_9\text{O}_6\text{Si} = 863.55$ ; found 864.49  $[\text{M}+\text{H}]^+$ .



**Intermediate 8.** (Lev-AMP). Intermediate **5** (5.0 g, 7.7 mmol) was dissolved in 50 mL THF followed by the addition of AMP (2.8 mL, 23.2 mmol). The reaction was stirred for 8 h at room temperature, after which the salts were filtered off and washed with THF. The solvent was removed by reduced-pressure evaporation and the product was purified by silica gel chromatography using 9:1-8:2 DCM:MeOH as the eluant. The product was isolated as a white solid (5.3 g, 94%).

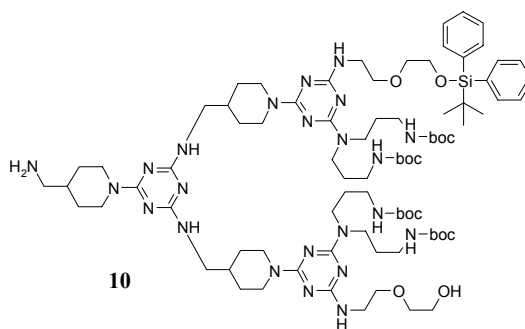
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 4.66 (br s, 2H), 4.16 (t,  $J = 4.64$  Hz, 2H), 3.60 (t,  $J = 4.64$  Hz, 2H), 3.54 (br, 6H), 3.01 (br, 4H), 2.86 (br, 2H), 2.78 (br, 2H), 2.69 (t,  $J = 6.47$  Hz, 2H), 2.53 (t,  $J = 6.47$  Hz, 2H), 2.12 (s, 3H), 2.03 (br, 1H), 1.66 (br, 4H), 1.37 (s, 18H), 1.18 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.59, 172.56, 164.32, 155.87, 78.90, 69.70, 68.68, 63.52, 44.81, 43.02, 40.33, 37.73, 37.50, 36.97, 34.42, 29.75, 29.29, 28.36, 27.75; MS (ESI) exact mass calcd for  $\text{C}_{34}\text{H}_{61}\text{N}_9\text{O}_8 = 723.46$ ; found 724.49  $[\text{M}+\text{H}]^+$ .





**Intermediate 9.** (Pyr-AMP). Pyridylcysteineamine hydrochloride (2.0 g, 9.0 mmol) was added to an ice-bath cooled flask containing 100 mL THF. DIEA (10.0 mL, 57.5 mmol) was added to the solution followed by cyanuric chloride (1.66 g, 9.0 mmol). The reaction was stirred for 2 h, followed by the addition of intermediate **2** (3.0 g, 9.1 mmol). The reaction was warmed to room temperature and stirred for 24 h. AMP (6.5 mL, 54.1 mmol) was then added to the reaction and stirred for an additional 8 h. The salts were filtered off and washed with THF. The solvent was removed by reduced-pressure evaporation and the residue was purified by silica gel chromatography using 9:1 DCM:MeOH with 1%  $\text{NH}_4\text{OH}$  as the eluant, giving the product as a white solid (5.9 g, 93%).

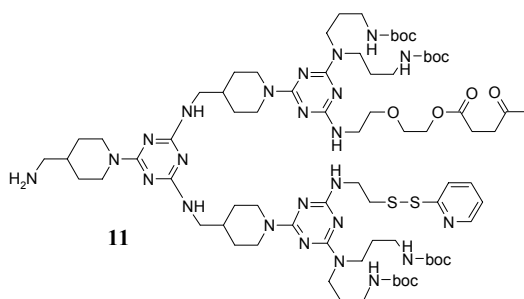
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ -1%  $\text{CD}_3\text{OD}$ ,  $\delta$ ): 8.32 (br, 1H), 7.60 (br, 1H), 7.55 (m, 1H), 7.00 (m, 1H), 4.58 (br, 2H), 3.55 (br, 2H), 3.38 (br, 4H), 2.93 (br, 4H), 2.88 (t,  $J = 6.47$  Hz, 2H), 2.64 (br m, 2H), 2.47 (d,  $J = 6.35$  Hz, 2H), 1.58 (br, 6H), 1.49 (br m, 1H), 1.30 (br s, 18H), 0.97 (br, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 165.42, 165.19, 164.35, 159.58, 155.77, 149.43, 136.78, 120.51, 119.48, 78.64, 47.34, 42.95, 41.97, 39.51, 38.96, 38.30, 37.96, 36.99, 36.79, 29.46, 28.28, 27.57; MS (ESI) exact mass calcd for  $\text{C}_{32}\text{H}_{54}\text{N}_{10}\text{O}_4\text{S}_2 = 706.38$ ; found 707.38  $[\text{M}+\text{H}]^+$ .



**Intermediate 10.** (TBDPS-Free OH-AMP). TBDPS-AMP (**7**) (4.046g, 4.7 mmol) was dissolved in 60 mL of THF at 0 °C. DIEA (3.0 mL, 17.2 mmol) was added to the cooled

solution followed by the addition of a solution of cyanuric chloride (863.3 mg, 4.7 mmol) in 10 mL THF. After stirring for 2 h a solution of FreeOH-AMP (**6**), (3.00g, 4.8 mmol) in 20 mL of THF was added and the solution was left to stir for 24 h at rt. AMP (6.0 mL, 49.9 mmol) was then added and the solution left to stir for 18 h. The salts were filtered off and washed with THF. The solvent was removed by reduced-pressure evaporation and the residue was dissolved in 100 mL DCM and washed with 100 mL of H<sub>2</sub>O followed by washing with 100 mL of brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, followed by filtration to remove the solids and reduced-pressure evaporation to remove the solvent. The product was isolated after silica gel chromatography using 9:1-8:2 DCM:MeOH as the eluant to give a white solid (7.7 g, 99%).

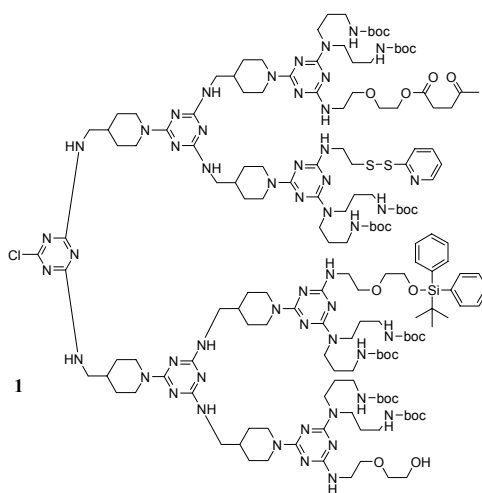
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.69 (m, 4H), 7.40 (m, 6H), 4.72 (br, 6H), 3.80 (t,  $J$  = 5.25 Hz, 2 H), 3.74 (t,  $J$  = 4.15 Hz, 2H), 3.60 (br m, 20H), 3.28 (br, 4H), 3.06 (br, 8H), 2.77 (br, 6H), 2.61 (d,  $J$  = 6.35 Hz, 2H), 1.87 (br, 2H), 1.77 (br, 6H), 1.71 (br, 8H), 1.55 (m, 1H), 1.44 (br s, 36H), 1.19 (m, 6H), 1.05 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>,  $\delta$ ): 165.79, 165.31, 164.47, 164.33, 156.10, 135.39, 133.39, 129.47, 127.47, 79.55, 78.99, 72.19, 72.06, 69.96, 69.75, 63.19, 61.26, 47.35, 45.87, 43.05, 42.97, 42.12, 40.43, 40.32, 40.23, 39.26, 36.94, 36.66, 29.70, 29.50, 28.25, 27.41, 26.59, 18.97; MS (MALDI-TOF) exact mass calcd for C<sub>83</sub>H<sub>139</sub>N<sub>23</sub>O<sub>12</sub>Si = 1678.07; found 1680.67 [M+H]<sup>+</sup>; MS (ESI) found 1679.04 [M+H]<sup>+</sup>, 840.01 [M+2H]<sup>2+</sup>.



**Intermediate 11.** (Lev-Pyr-AMP). Pyr-AMP (**9**) (3.6 g, 5.1 mmol) was dissolved in 60 mL of THF, and the solution was cooled in a salt/ice-bath. DIEA (3 mL, 17.3 mmol) was added to the cooled solution followed by the addition of cyanuric chloride (939 mg, 5.1 mmol). The solution stirred for 2 h, then Lev-AMP (**8**) (3.7 g, 5.1 mmol) in 20 mL THF was added and the solution stirred for an additional 18 h at rt. AMP (5 mL, 41.7 mmol) was added and the solution stirred

for an additional 18 h at rt. The salts were filtered off and washed with THF, followed by removal of the solvent by reduced-pressure evaporation. The residue was dissolved in 100 mL DCM and subsequently washed with 100 mL of H<sub>2</sub>O followed by 100 mL of brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> followed by filtration to remove the solids and reduced-pressure evaporation to remove the solvent. The product was isolated after silica gel chromatography using 9:1-8:2 DCM:MeOH as the eluant to give a white solid (6.5 g, 79%).

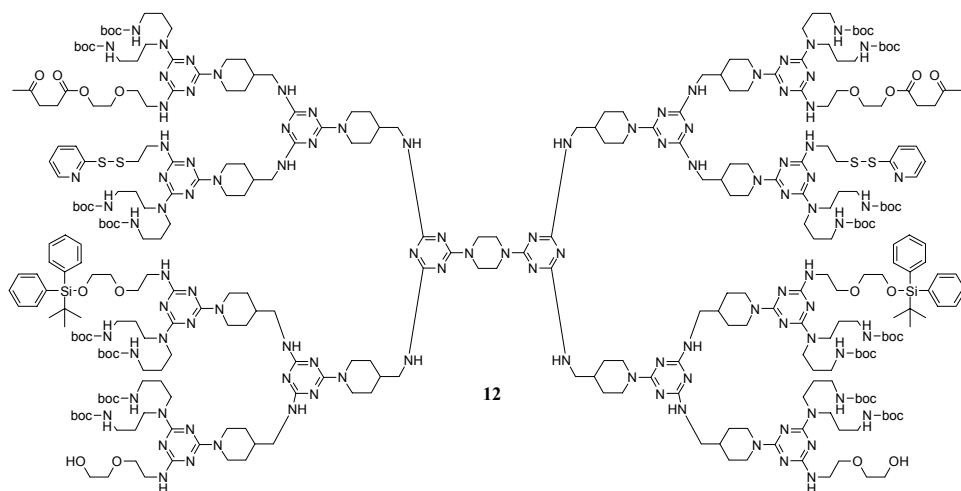
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>-1% CD<sub>3</sub>OD,  $\delta$ ): 8.43 (br, 1H), 7.61 (br, 1H), 7.56 (br, 1H), 4.63 (br, 6H), 4.17 (br, 2H), 3.61 (br, 2H), 3.55 (br, 8H), 3.45 (br, 4H), 3.36 (m, 2H), 3.20 (br, 4H), 3.00 (br, 8H), 2.70 (br, 2H), 2.70 (br, 8H), 2.62 (br, 2H), 2.55 (br, 2H), 2.13 (s, 3H), 1.72 (br m, 6H), 1.64 (br, 10H), 1.36 (br s, 36H), 1.10 (br, 12H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>,  $\delta$ ): 207.06, 172.73, 165.76, 165.29, 164.42, 164.34, 165.67, 156.08, 149.33, 137.07, 120.66, 119.64, 78.95, 69.94, 68.56, 63.54, 47.24, 45.82, 43.01, 42.25, 40.12, 39.08, 38.03, 37.65, 36.93, 30.22, 29.68, 29.60, 29.49, 28.24, 27.67, 27.49; MS (MALDI-TOF) average mass calcd for C<sub>75</sub>H<sub>126</sub>N<sub>24</sub>O<sub>12</sub>S<sub>2</sub> = 1620.12; found 1620.11[M+H]<sup>+</sup>.



**Dendron 1.** (FST-Cl). TBDPS-Free OH-AMP (**10**) (5.5 g, 3.3 mmol) was dissolved in 60 mL THF and the solution was cooled in an ice-bath. Hunig's base (2 mL, 11.5 mmol) was added to the solution followed by the addition of cyanuric chloride (604 mg, 3.3 mmol). The solution was stirred for 2 h followed by the addition of Lev-Pyr-AMP (**11**) (5.3 g, 3.3 mmol) in 20 mL THF. The solution was left to stir for 18 h at rt. The solvent was removed by reduced-pressure

evaporation. The residue was dissolved in 60 mL of DCM and washed with 100 mL of H<sub>2</sub>O followed by 100 mL of brine. The organic portion was dried over Na<sub>2</sub>SO<sub>4</sub>, followed by removal of the solvent by reduced pressure evaporation. The residue was purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant to give a white solid (10.6 g, 95%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ): 8.46 (br, 1H), 7.65 (m, 5H), 7.58 (m, 1H), 7.36 (m, 6H), 7.05 (m, 1H), 4.67 (br, 12H), 4.20 (t, *J* = 4.64 Hz, 2H), 3.77 (t, *J* = 5.25 Hz, 2H), 3.70 (br t, 2H), 3.63 (br t, 2H), 3.61-3.43 (br, 34H), 3.24 (br, 12H), 3.03 (br, 16H), 2.98 (br t, 2H), 2.72 (br m, 14H), 2.58 (t, *J* = 6.47 Hz, 2H), 2.16 (s, 3H), 1.80-1.60 (br, 34H), 1.41 (br s, 72H), 1.14 (br, 12H), 1.02 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ): 206.47, 172.56, 166.16, 165.76, 165.37, 164.52, 155.85, 149.55, 136.84, 135.41, 133.44, 129.46, 127.49, 120.59, 119.54, 78.74, 72.07, 69.98, 68.61, 63.51, 63.22, 61.41, 45.95, 43.00, 42.13, 40.46, 40.26, 37.72, 37.03, 29.72, 28.37, 27.73, 27.46, 26.66, 19.01; MS (MALDI-TOF) average mass calcd for C<sub>161</sub>H<sub>263</sub>ClN<sub>50</sub>O<sub>24</sub>S<sub>2</sub>Si = 3410.88; found 3410.50 [M+H]<sup>+</sup>.

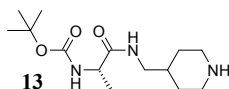


### Dendrimer 12. (FST-D)

FST-Cl (**1**) (500 mg, 0.15 mmol) was dissolved in 8 mL of THF. The solution was cooled in an ice-bath, followed by the addition of piperazine (75.8 mg, 0.88 mmol). The reaction stirred for 20 h. To the solution 10 mL of DCM was added, and the solution was washed with 5 mL of H<sub>2</sub>O, followed by 5 mL of sat. NaHCO<sub>3</sub>, and finally washed with 5 mL of

brine. The organic layer was passed through a plug of  $\text{Na}_2\text{SO}_4$  into a flask containing FST-Cl (**1**) (500 mg, 0.15 mmol). DIEA (0.1 mL, 0.58 mmol) was added to the reaction followed by 2 mL of MeOH. The reaction was left to stir for 24 h, and then 0.4 mL of Tween 20 was added along with an additional 0.4 mL DIEA. The reaction was left to stir at rt for 10 d. Piperazine (0.10 g, 1.16 mmol) was added to the solution to aid in purification of the dendrimer by reacting with any FST-Cl left in solution as the FST-Cl (**1**) and FST-D (**12**) appeared to have very similar  $R_f$ s by TLC. (The FST-piperazine intermediate has a much lower  $R_f$  than either **1** or **12**). The salts were removed by filtration and the solvent was removed by reduced-pressure evaporation. The off-white solid was dissolved in 8 mL of DCM, and purified by size-exclusion chromatography using Bio-Beads (SX-1, Bio-Rad) and DCM as the eluant. Fractions containing the dendrimer were combined, and concentrated followed by further purification with silica gel chromatography using 9:1 DCM:MeOH as the eluant to give a white solid (890 mg, 89%).

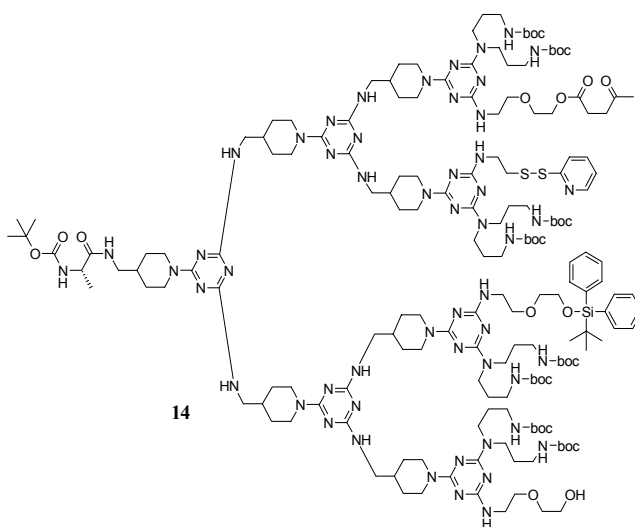
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 8.47 (br, 2H), 7.66 (m, 10H), 7.59 (m, 2H), 7.37 (m, 12H), 7.06 (m, 2H), 4.68 (br, 24H), 4.21 (t,  $J = 4.64$  Hz, 4H), 3.78 (t,  $J = 5.25$  Hz, 4H), 3.71 (br t, 4H), 3.64 (br t, 4H), 3.61-3.43 (br, 76H), 3.26 (br, 24H), 3.04 (br, 32H), 2.98 (br t, 4H), 2.73 (br m, 28H), 2.59 (t,  $J = 6.47$ , 4H), 2.17 (s, 6H), 1.80-1.60 (br, 68H), 1.40 (br s, 144H), 1.15 (br, 24H), 1.03 (s, 18H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 06.49, 172.6, 166.37, 165.85, 165.51, 164.56, 155.89, 149.6, 136.88, 135.46, 133.49, 129.51, 127.54, 120.63, 119.66, 78.81, 72.12, 70.03, 68.66, 63.56, 63.26, 61.43, 46.04, 43.05, 42.14, 40.51, 40.4, 40.31, 37.76, 36.99, 29.81, 29.77, 28.41, 27.78, 27.58, 26.71, 19.07; MS (MALDI-TOF) average mass calcd for  $\text{C}_{326}\text{H}_{534}\text{N}_{102}\text{O}_{48}\text{S}_4\text{Si}_2 = 6834.97$ ; found 6833.67  $[\text{M}+\text{H}]^+$ , 6855.52  $[\text{M}+\text{Na}]^+$ .



**tert-Butyl (S)-1-((piperidin-4-yl)methylcarbamoyl)ethylcarbamate, 13.** (BOC-Ala-AMP). In 30 mL of THF BOC-Ala-OSu (*N*-(*N*- $\alpha$ -*tert*-BOC-L-alanyloxy)succinimide) (2.0 g, 7.0 mmol) was added, followed by stirring and cooling the solution in an ice-bath. In 10 mL of THF AMP (2.52 mL, 21.0 mmol) was dissolved then added over 4 minutes to the solution containing BOC-Ala-OSu. The reaction was stirred for 2 h. The solution was filtered to remove the salts, and the

solvent was removed by reduced-pressure evaporation. The viscous liquid was dissolved in 50 mL DCM, and washed with 50 mL of H<sub>2</sub>O, followed by 50 mL of brine. The aqueous solution was back extracted with 50 mL of DCM. The organic fractions were combined and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was then filtered and the solvent removed by reduced-pressure evaporation, and the crude product further purified by silica gel chromatography using 8:2 DCM:MeOH with 1% NH<sub>4</sub>OH as the eluant to give a white solid (1.93 g, 97%).

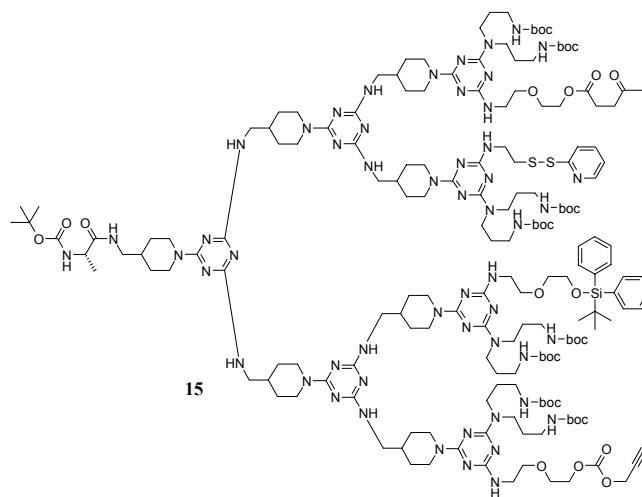
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ ): 4.08 (m, 1H), 3.06 (m, 2H), 3.00 (m, 2H), 2.53 (m, 2H), 1.63 (m, 2H), 1.58 (m, 1H), 1.32 (s, 9H), 1.24 (d,  $J$  = 6.84 Hz, 3H), 1.14 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>,  $\delta$ ): = 172.93, 155.42, 79.53, 77.25, 76.75, 49.83, 45.18, 44.66, 35.59, 29.49, 28.09, 18.44; MS (ESI) exact mass calcd for C<sub>14</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub> = 285.20; found 286.20 [M+H]<sup>+</sup>.



**Dendron 14.** (FST-Ala). FST-Cl (**1**) (1.0 g, 0.29 mmol) was dissolved in 20 mL of THF. In a separate vial BOC-Ala-AMP (**13**) (251.1 mg, 0.88 mmol) was dissolved in 10 mL of THF followed by addition of DIEA (0.20 mL, 1.2 mmol); this solution was then added to the solution containing FST-Cl. The solution was stirred for 2 d. The solvent was removed by reduced pressure evaporation and the residue purified by silica gel chromatography using 19:1 to 9:1 DCM:MeOH as the eluant to give a white solid (1.04 g, 97%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ ): 8.48 (br, 1H), 7.67 (m, 5H), 7.61 (m, 1H), 7.38 (m, 6H), 7.05 (m, 1H), 4.69 (br, 14H), 4.22 (t,  $J$  = 4.64 Hz, 2H), 4.12 (m, 1H), 3.79 (t,  $J$  = 5.25 Hz,

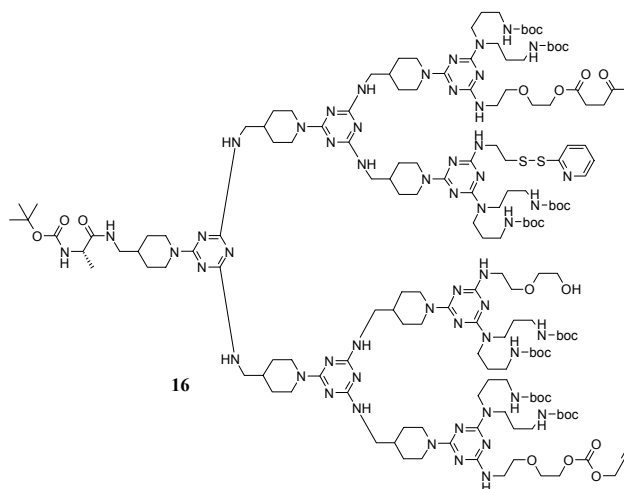
2H), 3.72 (br t, 2H), 3.65 (br t, 2H), 3.61-3.43 (br, 34H), 3.26 (br, 12H), 3.13 (br, 2H), 3.05 (br, 16H), 3.00 (br t, 2H), 2.74 (br m, 16H), 2.60 (t,  $J = 6.47$  Hz, 2H), 2.18 (s, 3H), 1.80-1.60 (br, 37H), 1.41 (br s, 81H), 1.33 (d,  $J = 7.08$  Hz, 3H), 1.16 (br, 14H), 1.03 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.39, 172.67, 172.49, 166.14, 165.84, 165.31, 164.47, 159.61, 155.79, 149.49, 136.79, 135.35, 133.38, 129.41, 127.44, 120.53, 119.48, 78.67, 72.17, 72.01, 69.89, 68.55, 63.45, 63.16, 61.27, 49.91, 45.9, 44.61, 42.95, 42.03, 40.4, 40.21, 37.65, 36.96, 29.66, 28.31, 28.11, 27.68, 27.52, 26.61, 18.96, 17.99; MS (MALDI-TOF) average mass calcd for  $\text{C}_{175}\text{H}_{289}\text{N}_{53}\text{O}_{27}\text{S}_2\text{Si} = 3659.81$ ; found 3658.73  $[\text{M}+\text{H}]^+$ .



**Dendron 15.** (FST-Ala-POC). In 10 mL of THF was dissolved FST-Ala (**14**) (950 mg, 0.26 mmol), followed by the addition of propargylchloroformate (0.036 mL, 0.36 mmol), and pyridine (0.059 mL, 0.73 mmol). The solution stirred for 2 h, and then the solvent was removed by reduced-pressure evaporation. The residue was purified by silica gel chromatography using 19:1 to 9:1 DCM:MeOH as the eluant to give a white solid (934 mg, 96%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 8.46 (br, 1H), 7.65 (m, 5H), 7.59 (m, 1H), 7.36 (m, 6H), 7.05 (m, 1H), 4.70 (d,  $J = 2.44$  Hz, 2H), 4.67 (br, 14H), 4.29 (t,  $J = 4.64$  Hz, 2H), 4.20 (t,  $J = 4.72$  Hz, 2H), 4.12 (m, 1H), 3.77 (t,  $J = 5.25$  Hz, 2H), 3.67 (br, 2H), 3.63 (br, 2H), 3.61-3.43 (br, 32H), 3.23 (br, 12H), 3.10 (br, 2H), 3.03 (br, 16H), 2.98 (br, 2H), 2.72 (br m, 16H), 2.58 (t,  $J = 6.47$  Hz, 2H), 2.53 (t,  $J = 2.44$  Hz, 1H), 2.15 (s, 3H), 1.80-1.60 (br, 37H), 1.39 (br s, 81H),

1.31 (d,  $J = 7.08$  Hz, 3H), 1.14 (br, 14H), 1.02 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.48, 172.56, 166.03, 165.43, 164.53, 159.63, 155.85, 154.39, 149.56, 136.84, 135.42, 133.45, 129.47, 127.50, 120.59, 119.54, 78.76, 75.72, 72.07, 69.99, 68.61, 68.40, 67.24, 63.52, 63.22, 55.17, 49.98, 45.98, 44.68, 43.01, 42.06, 40.46, 40.27, 37.72, 37.06, 29.73, 29.54, 28.37, 28.17, 27.74, 27.44, 26.67, 19.02, 17.98; MS (MALDI-TOF) average mass calcd for  $\text{C}_{179}\text{H}_{291}\text{N}_{53}\text{O}_{29}\text{S}_2\text{Si}$  = 3741.87; found 3741.68  $[\text{M}+\text{H}]^+$ .

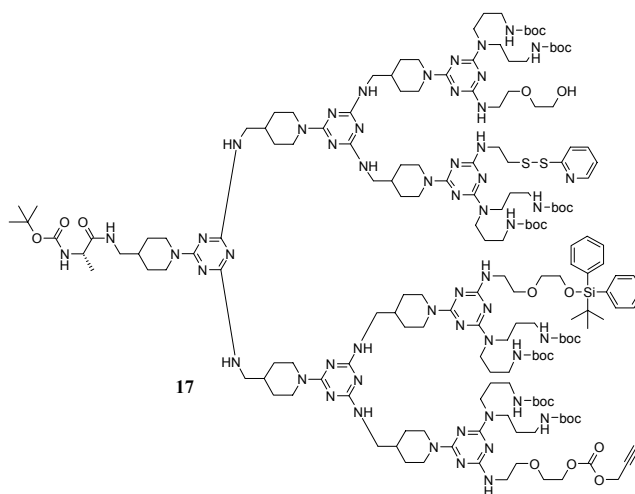


**Dendron 16.** (FST-Ala-POC/TBDPS). In 10 mL of THF was dissolved FST-Ala-POC (**14**) (250 mg, 0.067 mmol). Under a blanket of  $\text{N}_2$  was added 0.25 mL of a 1M tetrabutylammonium fluoride (TBAF) solution in THF (0.25 mmol). The solution stirred for 4 h, followed by removal of the solvent by reduced-pressure evaporation. The residue was purified by size-exclusion chromatography using Bio-Beads (SX-1, Bio-Rad) and DCM as the eluant. The product was further purified by silica gel chromatography using 19:1 to 9:1 DCM:MeOH as the eluant to give a white solid (210 mg, 90%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 8.49 (br, 1H), 7.67 (m, 1H), 7.62 (m, 1H), 7.09 (m, 1H), 4.74 (d,  $J = 2.44$  Hz, 2H), 4.70 (br, 14H), 4.32 (t,  $J = 4.64$  Hz, 2H), 4.23 (t,  $J = 4.72$  Hz, 2H), 4.13 (m, 1H), 3.73 (br t, 2H), 3.70 (br t, 2H), 3.63 (br t, 2H), 3.61-3.43 (br, 34H), 3.27 (br, 12H), 3.14 (br, 2H), 3.06 (br, 16H), 3.00 (br t, 2H), 2.75 (br m, 16H), 2.61 (t,  $J = 6.47$  Hz, 2H), 2.50 (t,  $J = 2.44$  Hz, 1H), 2.19 (s, 3H), 1.80-1.60 (br, 37H), 1.42 (br s, 81H), 1.35 (d,  $J = 7.08$  Hz, 3H), 1.17 (br, 14H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.60, 172.70, 165.87, 165.52,



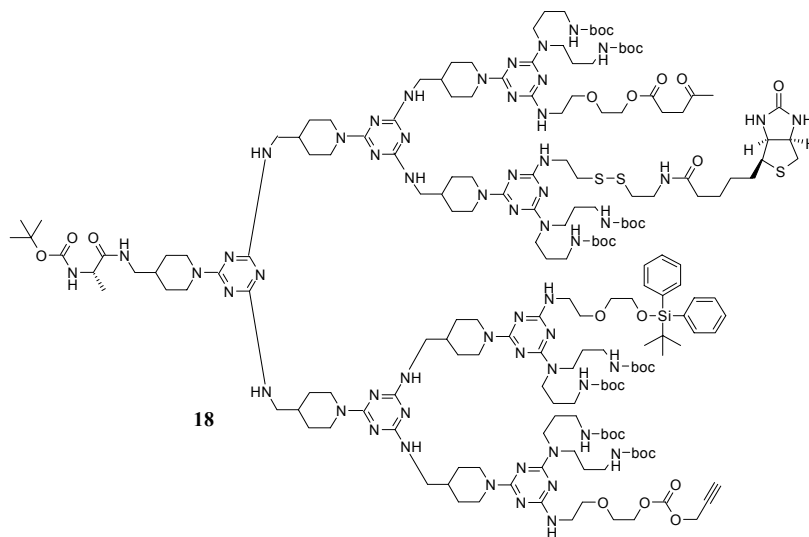
164.64, 156.01, 154.51, 149.69, 136.95, 120.72, 119.71, 78.92, 75.78, 72.23, 70.13, 68.74, 68.52, 67.37, 63.65, 61.60, 55.29, 50.09, 46.08, 44.79, 43.13, 42.18, 40.39, 37.84, 37.09, 29.85, 29.64, 28.48, 28.27, 27.85, 27.55, 18.04; MS (MALDI-TOF) average mass calcd for  $C_{163}H_{273}N_{53}O_{29}S_2 = 3503.46$ ; found 3503.22  $[M+H]^+$ .



**Dendron 17.** (FST-Ala-POC/Lev). FST-Ala-POC (**14**) (50 mg, 0.013 mmol) was dissolved in 5 mL of THF. In another 5 mL of THF was added 5 drops of anhydrous hydrazine. Portions of the solution containing hydrazine were added over 2 h, while monitoring the reaction by TLC. The reaction appeared complete after the addition of 3 mL of the hydrazine solution. The solvent was then removed by reduced-pressure evaporation, and the residue purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant, giving a white solid (45 mg, 92%).

$^1H$  NMR (500 MHz,  $CDCl_3$ ,  $\delta$ ): 8.50 (br, 1H), 7.69 (m, 5H), 7.62 (m, 1H), 7.39 (m, 6H), 7.09 (m, 1H), 4.74 (d,  $J = 2.44$  Hz, 2H), 4.70 (br, 14H), 4.32 (t,  $J = 4.64$  Hz, 2H), 4.13 (m, 1H), 3.80 (t,  $J = 5.25$  Hz, 2H), 3.74 (br t, 2H), 3.70 (br t, 2H), 3.61-3.43 (br, 34H), 3.28 (br, 12H), 3.14 (br, 2H), 3.06 (br, 16H), 3.01 (br t, 2H), 2.76 (br, 14H), 2.55 (t,  $J = 2.44$  Hz, 1H), 1.80-1.60 (br, 37H), 1.42 (br s, 81H), 1.35 (d,  $J = 7.08$  Hz, 3H), 1.17 (br, 14H), 1.05 (s, 9H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ,  $\delta$ ): 166.43, 165.99, 165.55, 164.67, 155.97, 154.52, 149.71, 136.95, 135.56, 133.60, 129.59, 127.62, 127.20, 120.72, 119.87, 78.94, 75.78, 72.21, 70.13, 68.54, 67.38, 63.35, 61.64, 55.30, 50.11, 46.10, 44.81, 43.15, 42.14, 40.60, 40.43, 37.12, 29.90, 29.67,

28.50, 28.29, 27.67, 26.80, 19.16, 18.01; MS (MALDI-TOF) average mass calcd for  $C_{174}H_{285}N_{53}O_{27}S_2Si$  = 3643.76; found 3643.86  $[M+H]^+$ .



**Dendron 18.** (FST-Ala-POC-Biotin). In 8 mL of DCM was dissolved FST-Ala-POC (**14**) (200 mg, 0.053 mmol). To this solution was added dithiothreitol (DTT) (50 mg, 0.32 mmol), whereupon the reaction began to turn yellow. The solution was stirred under a blanket of  $N_2$  at rt for 2 h. The solution was directly applied to a size exclusion column (Bio-Beads S-X1, Bio-Rad) using DCM as the eluant. The first fractions containing a UV active compound were added directly to a solution of Biotin-PCA (Biotinpyridyldisulfidecysteineamine) (50 mg, 0.12 mmol) in 5 mL of DMF. The solution immediately began to turn yellow and the solution was concentrated to 6 mL by passing a stream of dry  $N_2$  over the reaction vessel, and then left to stir under a blanket of  $N_2$  for 2h. The solution was further concentrated by passing a stream of dry  $N_2$  over the sample. The solution was then applied to a size exclusion column (Bio-Beads S-X1, Bio-Rad) using DCM as the eluant. Fractions containing the initial UV-active sample were combined, and the solvent removed using reduced-pressure evaporation. The residue was further purified by silica gel chromatography using 9:1 DCM:MeOH as the eluant to give a white solid (185 mg, 88%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.66 (m, 4H), 7.37 (m, 6H), 4.71 (d,  $J = 2.44$  Hz, 2H), 4.69 (br, 14H), 4.44 (m, 1H), 4.29 (br t, 2H), 4.25 (m, 1H), 4.20 (br t, 2H), 4.13 (m, 1H), 3.78 (t,  $J = 5.13$  Hz, 2H), 3.67 (br t, 2H), 3.64 (br t, 2H), 3.61-3.43 (br m, 32H), 3.24 (br, 12H), 3.10 (br, 5H), 3.04 (br, 16H), 2.86 (m, 4H), 2.82-2.62 (br m, 18H), 2.59 (t,  $J = 6.47$  Hz, 2H), 2.54 (t,  $J = 2.44$  Hz, 1H), 2.16 (br s, 5H), 1.80-1.60 (br, 37H), 1.60-1.5 (m, 4H), 1.40 (br s, 83H), 1.32 (d,  $J = 7.08$  Hz, 3H), 1.15 (br m, 14H), 1.02 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 206.55, 173.12, 172.61, 166.32, 165.80, 165.46, 164.56, 164.49, 163.68, 155.89, 154.42, 135.45, 133.49, 129.50, 127.53, 78.80, 75.74, 72.11, 70.12, 70.03, 68.65, 68.44, 67.28, 63.56, 63.26, 61.79, 61.67, 60.00, 59.88, 55.43, 55.21, 49.97, 46.02, 44.71, 43.07, 41.93, 40.50, 40.39, 40.32, 40.19, 38.06, 37.95, 37.76, 37.56, 37.01, 36.84, 36.71, 36.57, 35.58, 29.80, 29.77, 29.59, 28.40, 28.21, 28.04, 27.97, 27.78, 27.54, 26.70, 25.28, 19.05, 18.12; MS (MALDI-TOF) average mass calcd for  $\text{C}_{186}\text{H}_{307}\text{N}_{55}\text{O}_{31}\text{S}_3\text{Si} = 3934.15$ ; found 3934.03  $[\text{M}+\text{H}]^+$ .

## CHAPTER IV

### INCORPORATION OF A SHORT LINKER INTO MELAMINE DENDRIMERS: RAPID ACCESS TO UNIQUE MOLECULES

#### 4.1 Introduction

Dendrimers have been pursued academically and commercially since their inception for potential applications. While current commercial applications are limited a steady increase in the number of patents filed dealing with dendrimers indicates efforts to identify a niche they may be applied to. More than a thousand patents related to dendrimers are projected to be granted between the years 2001 and 2005, up from 51 patents granted a decade earlier.<sup>212</sup> The pursuit of dendrimers as functional materials stems from their possession of unique physical properties not found with linear polymers or other materials. The cause of many of these unique properties is attributed to the highly branched nature of the macromolecules.<sup>213</sup>

The volume occupied by a dendrimer in solution increases cubically with an increase in generation; while in contrast the mass increases exponentially with subsequent generations. Therefore, solution properties of dendrimers deviate from those of linear counterparts. Comparison of macromolecules with exactly the same number of repeat units arranged either in a branched or linear sequence reveal surprising differences between the two structures.<sup>214</sup> Dendrimers generally show lower viscosities, smaller hydrodynamic radii, and better solubility properties than exact linear analogs.

Considerable effort has been applied to the identification of dendrimers with unique properties for material applications. Some applications of unique dendrimer materials include light harvesting<sup>215</sup>, gadolinium III-chelated PAMAM dendrimers for magnetic resonance imaging,<sup>216</sup> catalysis using dendrimer encapsulated nanoparticles,<sup>217</sup> tissue engineering,<sup>218</sup> gene transfection reagents,<sup>219</sup> and drug delivery (Chapter V).<sup>220</sup>

A series of melamine dendrimers were constructed containing the two atom linkage molecule hydrazine. The syntheses of these molecules proved to be rapid, requiring little effort for their purification, and tractable at moderate scales exceeding 5 grams of product. Originally pursued as precursors to azo dendrimers, the resulting oxidized products proved to labile to isolate and characterize. The incorporation of a short linker however provides a series of dendrimers with limited flexibility and thus a rigid structure. Rigid dendrimers, or shape

persistent dendrimers, have recently found use in conformational studies<sup>221</sup> and the production of novel polycyclic aromatic hydrocarbons.<sup>222</sup> The low carbon to nitrogen (C:N) ratio of these compounds may lend themselves to studies in the production of carbon nitride materials.<sup>149</sup>

Dendrimers can be considered flexible molecules and the use of such descriptors as surface groups is somewhat of a misnomer. Studies have shown that dendrimers of sufficiently large generations, generally four or greater assume a globular structure. However the location of dendrimers surface groups is debated.<sup>223</sup> The incorporation of rigid linkers limits the conformational mobility of the dendrimer structure providing fewer degrees of rotation. It has been conclusively shown using a shape persistent dendrimer that the surface groups of rigid dendrimers are truly found at the surface.<sup>221</sup>

## 4.2 Rationale

Macromolecules containing azobenzene linkage groups have been pursued in the field of polymer and dendrimer chemistry for sometime. The motivation for incorporating azo linkages into materials stems from the facile cis to trans isomerization of azobenzenes. Incorporating the azo linkage into macromolecules is done in hopes of producing novel photo-responsive materials. It was proposed that using hydrazine as a linker, followed later by oxidation of the linker to an azo group, would provide a route to the site specific incorporation of azo groups into melamine dendrimers. An additional motivation was to produce a dendrimer where every linking group was an azo functionality. It was found that oxidation of hydrazine linked triazines to azo groups was not facile as has previously been reported,<sup>224</sup> but results in decomposition of the starting material.

The monochlorotriazine containing two piperidines at the surface can readily be obtained in high yields and is easily purified by recrystallization. The lack of an N-H bond contributed by the surface group was attractive for potential UV studies, where the loss of the N-H bonds corresponding to oxidation of the hydrazine could be monitored, without overlapping peaks from the surface groups. The inability to produce clean oxidation products made the lack of N-H bonds on the surface group irrelevant. However, the piperidines did impart physical properties to the dendrimers which greatly aided their purification.

The route to the synthesis of the dendrimers was convergent and the products could be readily purified by recrystallization from or precipitation with methanol. The later generations

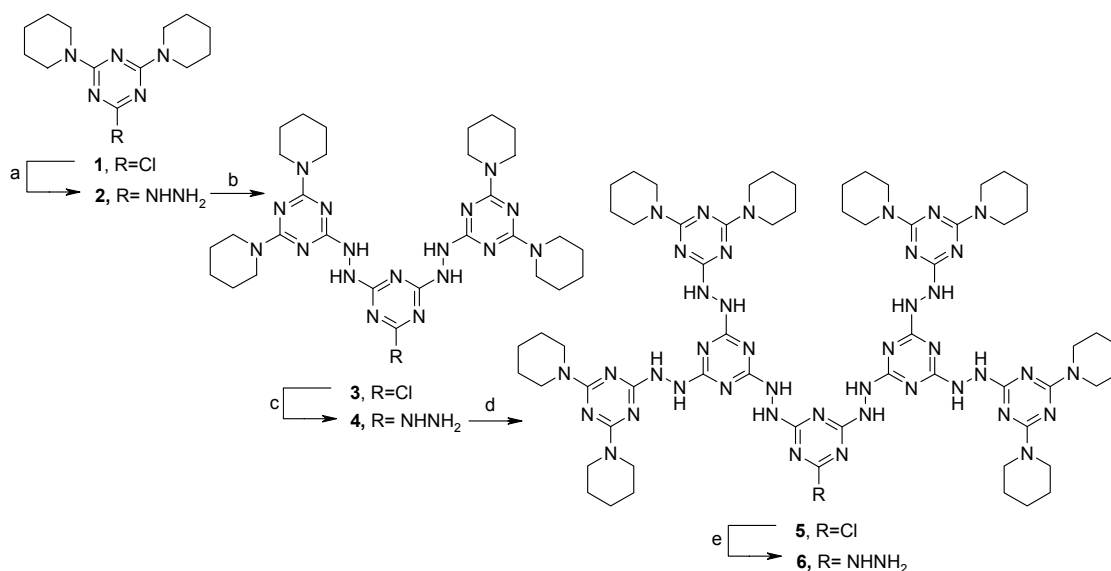
were purified through precipitating the product from the reaction solution with methanol and further washing with hot methanol or acetonitrile.

### 4.3 Materials and Methods

The surface group containing two piperidines and a monochlorotriazines was readily synthesized on a moderate scale with the product purified by recrystallization using either methanol or ethyl acetate. The synthesis of 78.5 grams of **1** was carried out by careful substitution of two positions of cyanuric chloride with piperidine. The solution was cooled in a dry ice/isopropanol bath for two reasons. First the reaction is exothermic and on such a large scale the reaction could readily get out of hand. Second, the reaction of piperidine with monochlorotriazines is rapid, and all three positions of cyanuric chloride can be substituted with piperidine in a few hours at 0 °C if enough equivalents of the amine are present. To ensure only disubstitution of cyanuric chloride the reaction was initiated at -78 °C with slow addition of piperidine and Hunig's base (DIEA, diisopropylethylamine) to the THF solution of cyanuric chloride. Completion of the reaction was followed with removal of the salts by filtration, reduced pressure evaporation of the solvent and recrystallization of the crude material from ethyl acetate or methanol. A white crystalline product was obtained upon cooling the solution.

Subsequent steps of the dendrimer syntheses were conducted through the iterative reaction of hydrazine with a monochlorotriazine (Figure 4.1 steps a, c, e), and reaction of the hydrazine terminated dendron with half and equivalent of cyanuric chloride to provide the monochlorotriazine (Scheme 4.1, steps b and d).

The purification of **1** and **2** was accomplished through recrystallization of the crude material from hot methanol. The products are readily soluble in THF, DCM and chloroform. Dendrons **3** and **4** are not appreciably soluble in DCM or chloroform, but dissolve slightly in solutions of THF at elevated temperatures. Concentrations of the monochlorotriazine **3** in CDCl<sub>3</sub> suitable for NMR analysis could not be obtained. The hydrazine analog **4** dissolved in CDCl<sub>3</sub> at a sufficient concentration to obtain a satisfactory <sup>13</sup>C NMR spectrum after several hours. Dendrons **5** and **6** are readily soluble in DCM and THF, however the hydrazine terminated dendron **6** is less so than the monochlorotriazine **5**. None of the dendrons **3-6** are soluble to any appreciable extent in hot methanol or acetonitrile. Reactions were worked-up and the products purified by addition of methanol to the reaction, heating the solution followed by filtration of the hot solvent to isolate the products as a white powder.

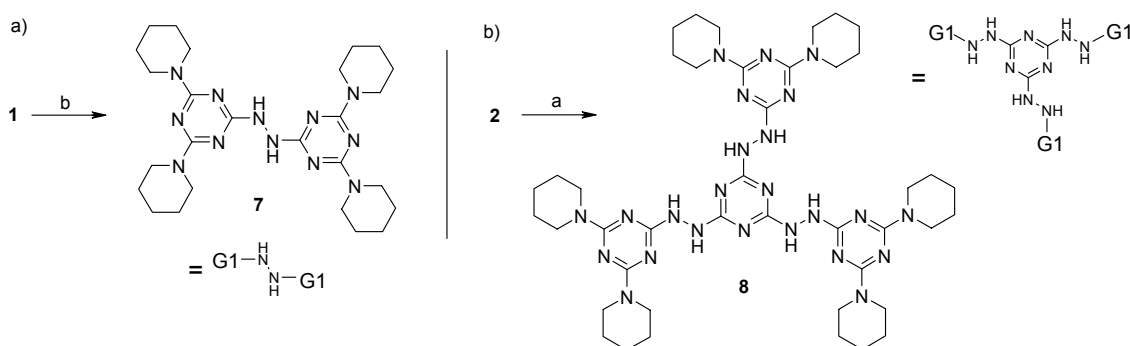


**Scheme 4.1.** Synthesis of hydrazine dendrons. a) Hydrazine, THF, 80 °C, 8 h, 96%; b) CC, DIEA, THF, 0 °C→rt, 18 h, 96%; c) hydrazine, THF, 80 °C, 24 h, 83%; d) CC, DIEA, THF, 0 °C→40 °C, 24 h, 95%; e) hydrazine, THF, 80 °C, 24 h, 96%. CC = Cyanuric chloride; DIEA = Hunig's base, diisopropylethylamine.

The resulting six dendrons were utilized in the synthesis of a series of dendrimers. Two strategies were devised which would each result in the synthesis of a dendrimer. The reactions depicted in Scheme 4.1 are illustrative of the approach. Reaction of a hydrazine terminated dendron (**2**) with the monochlorotriazine of the same generation (**1**) gave what is referred to as the G1-Hyd-dimer (**7**), the dimer of two G1 dendrons linked by hydrazine (Scheme 4.2a). The reaction proceeds through substitution of the monochlorotriazine of one dendron by the hydrazine of the other to give the product **7**. The second strategy was the substitution of three hydrazine terminated dendrons around a cyanuric chloride core. One equivalent of cyanuric chloride was mixed with three equivalents of the hydrazine terminated dendron **2**, and after prolonged heated resulted in the G1-Hyd-trimer **8**; three G1 dendrons linked to a triazine core through hydrazine linkers (Scheme 4.2b).

The reactions producing **7** and **8** were sluggish, and TLC analysis during the course of the reaction showed slow consumption of the starting materials. Steric congestion around the reaction centers resulting from the use of short linkers is one factor which may contribute to the retarded rate of reaction. The languid reaction may also be due to electronic effects, stemming

from a reduced nucleophilicity of the hydrazine resulting from electron donation into the triazine ring. It was necessary to heat the reactions to 105 °C for 36 hours to achieve any appreciable yield.

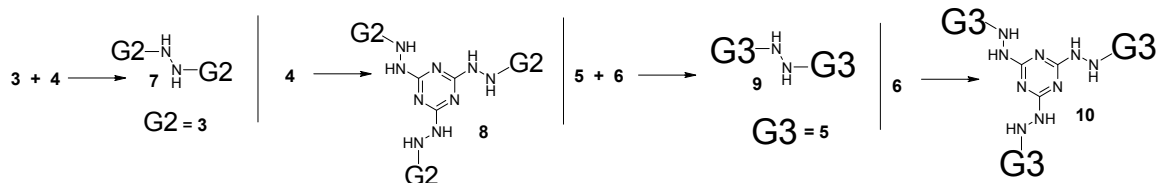


**Scheme 4.2.** Syntheses of a G1-hydrazine linked dimer and trimer. a) **2**, THF, 105 °C, 36 h, 66%; b) cyanuric chloride, THF, 105 °C, 36 h, 52%.

The isolation of the products **7** and **8** from the crude reaction turned out to be trivial. Dendrimers **7** and **8** are not soluble in hot methanol while the starting materials and other side products were. Following removal of the solvent from the crude reaction, methanol was added. Subsequent heating of the solution results in the suspension of a fine white powder, which is isolated after filtration of the hot solution. Although isolated in only moderate yield, the products **7** and **8** appear as a single spot by TLC analysis, give one molecular ion peak using ESI-MS, and appear clean by  $^{13}\text{C}$  and  $^1\text{H}$  NMR analysis.

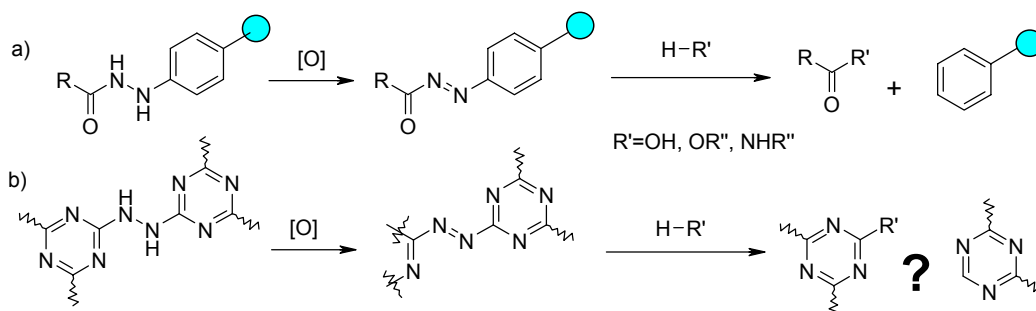
Construction of higher generation dendrimers was not completely successful. Utilizing the methods described above attempts made to construct the G2-Hyd-dimer and G2-Hyd-trimer as well as the G3 analogs did not provide clean products (Scheme 4.3). ESI-MS of the crude material revealed peaks with  $m/z$  ratios corresponding to those of the putative products.





**Scheme 4.3.** Outline of the synthetic route to higher generation hydrazine linked triazine dendrimers. In the first and third columns coupling of a monochlorotriazine dendron with a hydrazine terminated dendron gives the corresponding dimer. In the second and fourth column substitution by three hydrazine terminated dendrons with cyanuric chloride results in the corresponding trimer.

The goal at the outset of this project was to construct azo linkages through the oxidation of the corresponding hydrazine. Several reagents, including  $\text{KMnO}_4$ ,  $\text{H}_2\text{O}_2$ , *N*-bromosuccinimide, bleach, and  $\text{FeCl}_3$ , were tried to effect the oxidation, but none were satisfactory in producing the desired products. In several cases it appeared the oxidation resulted in decomposition of the dendrimer to unknown products. Later it was realized that the structural similarity between the hydrazine dendrons and aryl hydrazines could explain the decomposition of the starting materials. Aryl hydrazines have been used as linkers on the solid phase for the synthesis of amides, esters, and acids. Acylation of an aryl hydrazine, followed by mild oxidation produces the aryl diazene which readily decomposes under mild conditions to give arenes and nitrogen (Scheme 4.4a).<sup>225</sup> The nature of the products obtained after oxidation of the hydrazine dendrimers is unknown, but the structural similarity between aryl hydrazides and the azo linked triazine offers a plausible explanation for the observed decomposition (Scheme 4.4b).



**Scheme 4.4.** Structural similarities between arylhydrazides and hydrazine linked triazines. The similarities may explain the dendrimers susceptibility to degradation under oxidative conditions.

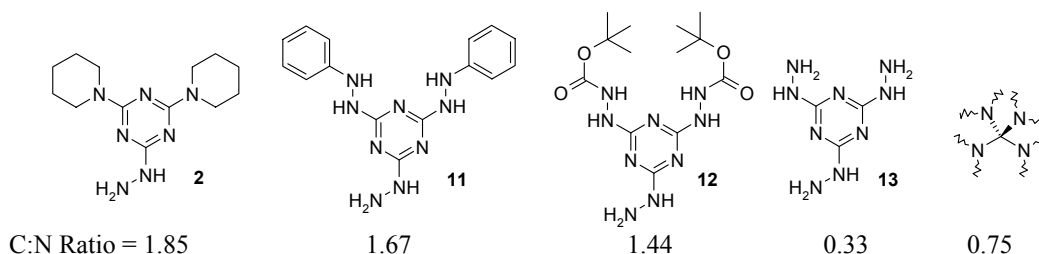
#### 4.4 Conclusions

The construction of the dendrons **1-6** proceeded rapidly and in high yields, with purification using recrystallization or precipitation and washing with methanol. Efforts to construct larger dendrimers were frustrated by incomplete reactions. Mass spectral analysis of the crude reactions identified peaks corresponding to the desired products, but the reactions could not be forced to completion. However, the synthesis of generation 1 dendrons was realized. Efforts to form dendrimers using the bifunctional linker piperazine, and dimerizing the monochlorotriazines met with some success but the reactions remain to be optimized and the products fully characterized.

These materials exhibited several unique properties which are not fully understood. The series of molecule exhibits an interesting solubility trend in organic solvents as described above. The series of dendrons and dendrimers turn various colors including green, purple, yellow and red upon addition of a strong base such as sodium methoxide to a solution in which they are dissolved. Attempts to remove a slight yellow color from a solution of **8** using activated charcoal resulted in an increase in the intensity of the color. Mass spectral analysis of the corresponding sample revealed the appearance of a species containing two less protons than the original sample, presumably from the oxidation of the hydrazine. This hypothesis is not entirely unreasonable as activated charcoal results in the oxidation of hydrogen sulfide gas upon its adsorption.<sup>226</sup> Metal complexation by these materials was investigated, and mass spectral analysis of **8**, incubated with FeCl<sub>3</sub> reveals a product corresponding to **8** plus several iron species.

Initial attempts to get NMR spectra of the samples resulted in the immediate production of a deep yellow colored solution upon addition of CDCl<sub>3</sub>. It was discovered the deuterated solvent was rather old and chloroform is known to decompose over time, producing phosgene. Newer samples of CDCl<sub>3</sub> did not result in the yellow solution and the samples remained clear and colorless.

The C:N ratio of the dendrons can be decreased, meaning a higher N content, through replacement of the surface piperidines with molecules containing less carbon or more nitrogen (Figure 4.1). Phenylhydrazine has been attached to the triazine (**11**) as well as BOC-hydrazine (**12**), but these molecules have not been incorporated into higher dendrons or dendrimers.



**Figure 4.1.** The C:N ratio of various substituted triazines. The ratio can be decreased by the incorporation of phenyl hydrazine at the surface (**11**), or the BOC-protected hydrazine (**12**). Removal of the BOC groups reveals the known compound **13**. The C:N ratio between molecules is compared to the theoretical carbon nitride species (C<sub>3</sub>N<sub>4</sub>, far right) with a C:N ratio of 0.75.

The synthesis of melamine dendrons containing the hydrazine linker is efficient, producing dendrons in good yield on a multi-gram scale. The efficiency of the reaction sequence is aided by the trivial purification of these materials using recrystallization or precipitation, resulting in a variety of dendron building blocks with interesting, but as of yet not understood properties.

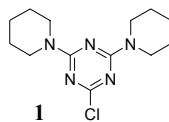
#### 4.5 Experimental: Preparation and Characterization

Solvents used were of reagent grade. THF was stored over 4Å molecular sieves. Piperidine (Advanced Chemtech), cyanuric chloride (Acros), hydrazine (anhydrous), and piperazine (Aldrich) were used as received from suppliers. Reactions conducted at elevated temperature were contained in a pressure flask (Chemglass).

NMR spectra were obtained from the use of a Varian Mercury 300 MHz spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported as δ (ppm = parts per million) relative to the residual solvent peak appearing from the deuterated solvent used. Thin-layer chromatography (TLC) was performed using EMD silica gel 60 F<sub>254</sub> pre-coated plates (0.25 mm). Flash chromatography was performed using EMD silica gel 60 (0.040 mm particle size). All compounds were judged pure by TLC analysis (single spot/ two solvent systems) using a UV lamp and/or ninhydrin staining. All mass spectral analyses were carried out by the Laboratory for Biological Mass Spectrometry (LBMS) at Texas A&M.

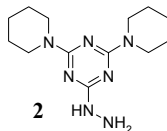
**Caution:** Hydrazine is a known carcinogen and care should be taken in handling it. It is recommended that glassware and equipment which come in contact with it be rinsed with a

bleach solution. This procedure oxidizes the hydrazine to N<sub>2</sub>, but care should be exercised as the reaction can rapidly evolve gas.



**2-Chloro-4,6-di(piperidin-1-yl)-1,3,5-triazine** (Intermediate **1**). Cyanuric chloride (56.0 g, 304 mmol) was dissolved in 500 mL of THF. The flask was cooled in a dry ice/acetone bath. Piperidine (60 mL, 608 mmol) was mixed with Hunig's base (DIEA, diisopropylethylamine), (110 mL, 634 mmol) and added slowly over five minutes to the cooled solution of cyanuric chloride while stirring vigorously. A white ppt. formed immediately. After complete addition of the piperidine/DIEA 40 mL of methanol was added. The solution was removed from the dry ice/acetone bath and stirred for an additional 6 h. The salts formed during the reaction were removed by filtration and washed with THF. The solvent was removed by reduce-pressure rotary evaporation. The crude product was dissolved in a minimal amount of hot methanol. The solution slowly cooled to room temperature and then placed in a refrigerator for overnight. The solid was collected as a white crystalline solid (78.5 g, 92% yield).

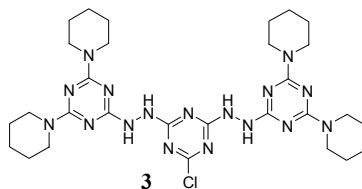
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 3.70 (m, 8H), 1.62 (m, 4H), 1.55 (m, 8H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, δ): 169.35, 163.99, 44.31, 25.57, 24.55; MS (ESI-TOF) exact mass calcd for C<sub>13</sub>H<sub>20</sub>ClN<sub>5</sub> = 281.14; found 282.15 [M+H]<sup>+</sup>.



**1-(4,6-Di(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazine** (Intermediate **2**). In 50 mL of THF in a pressure flask was dissolved **1** (10.0 g, 35.5 mmol). Anhydrous hydrazine (4.5 mL, 143 mmol) was added to the solution and the pressure flask was sealed. The solution was heated in an oil bath at 80 °C for 8 h. Upon cooling two layers formed, with the bottom layer primarily

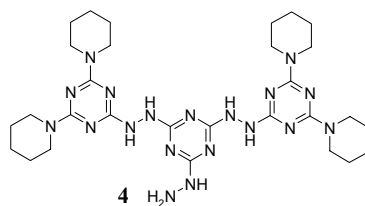
composed of hydrazine. The bottom layer was removed with a pipette, and the remaining solution was transferred to a round bottom flask. The solvent was removed by reduced-pressure rotary evaporation. The crude product was dissolved in hot methanol and slowly cooled to room temperature, following by placing the flask in a refrigerator for several hours, providing a white ppt. The product was isolated as a white powder (9.45 grams, 96%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 6.20 (s, 1H, *NH*), 3.91 (s, 2H, *NH*), 3.70 (m, 8H), 1.60 (m, 4H), 1.53 (m, 8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 168.89, 164.70, 43.92, 25.69, 24.83; MS (ESI-TOF) exact mass calcd for  $\text{C}_{13}\text{H}_{23}\text{N}_7$  = 277.20; found 278.20  $[\text{M}+\text{H}]^+$ .



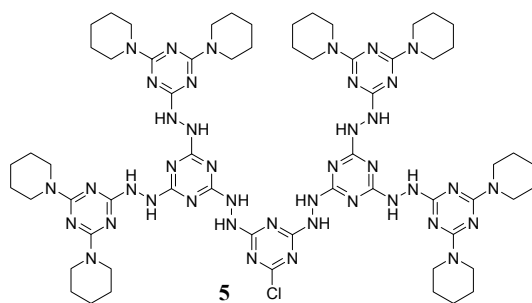
**Dendron 3.** In 200 mL of THF was dissolved intermediate **2** (12.0 g, 43.3 mmol). The solution was cooled in an ice bath. Cyanuric chloride (4.00 g, 21.7 mmol) was added to the solution, followed by addition of DIEA (15.0 mL, 86.8 mmol). The reaction was warmed to room temperature and stirred for 18 h. The solvent was removed by reduced-pressure rotary evaporation, followed by addition of ~50 mL of hot methanol to the clear tar-like material. The solution was sonicated, and the appearance of a white ppt became evident. After the tar-like material gave way to a white ppt, the solution was again heated, and the product isolated as a white powder by hot filtration (13.8 g, 96%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 3.66 (m, 16H), 1.61 (m, 8H), 1.51 (br, 16H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 167.41, 165.93, 164.43, 44.10, 25.73, 24.87;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 9.47-9.30 (m, 2H, *NH*), 8.69-8.63 (m, 2H, *NH*), 3.64-3.57 (m, 16H), 1.55 (br s, 8H), 1.43 (br s, 16H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 169.84, 168.67, 168.34, 167.81, 167.77, 167.26, 167.07, 166.97, 166.73, 164.80-164.20, 43.44, 25.41, 24.46; MS (ESI-TOF) exact mass calcd for  $\text{C}_{29}\text{H}_{44}\text{ClN}_{17}$  = 665.37; found 666.37  $[\text{M}+\text{H}]^+$ , 333.69  $[\text{M}+2\text{H}]^{2+}$ .



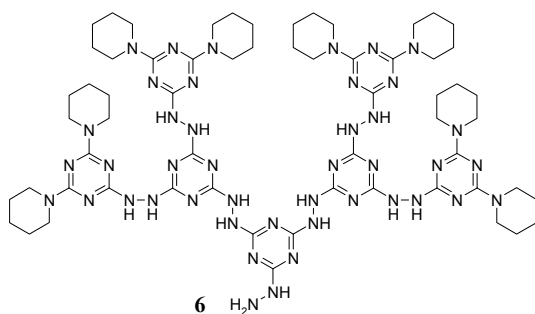
**Dendron 4.** In a pressure flask was placed dendron **3** (10.0 g, 15.1 mmol) and 200 ml of THF. To the suspension was added hydrazine (2.5 mL, 76.6 mmol), the reaction sealed and heated in an oil bath at 80 °C for 24 h. Upon cooling two layers formed, the bottom primarily containing hydrazine, which was removed by pipette. The solution was transferred to a round bottom flask and the solvent removed by reduced-pressure rotary evaporation. The reaction was purified by washing the residue in hot methanol, and collecting the white powder after the solution cooled (8.24 g, 83%). This product was also synthesized in a one pot sequence beginning with intermediate **2** (4.00 g, 14.4 mmol) and reaction with ½ equivalent of cyanuric chloride (1.33 g, 7.20 mmol) with DIEA (3 mL, 17.3 mmol). Upon completion of the reaction as visualized by TLC excess hydrazine was added and the reaction heated at 105 °C for 12 h. The product was isolated by filtration of the solution and washing the ppt with methanol, THF, and H<sub>2</sub>O (3.87 g, 81%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ): 8.40-8.20 (br, 4H, *NH*), 8.05-7.95 (br, 1H, *NH*), 4.05 (br, 2H, *NH*), 3.61 (br s, 16H), 1.55 (br s, 8H), 1.41 (br s, 16H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 167.83, 167.64, 167.36, 164.62, 164.38, 43.38, 25.40, 24.44; MS (ESI-TOF) exact mass calcd for C<sub>29</sub>H<sub>47</sub>N<sub>19</sub> = 661.43; found 662.40 [M+H]<sup>+</sup>, 331.72 [M+2H]<sup>2+</sup>.



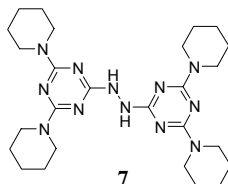
**Dendron 5.** In a round bottom flask with 100 mL of THF was added dendron 4 (6.00 g, 9.07 mmol). The solution was cooled in an ice bath and cyanuric chloride (836 mg, 5.43 mmol) was added to the solution, followed by slow addition of DIEA (3 mL, 17.3 mmol). The reaction slowly warmed to room temperature and then heated at 40 °C for 24 h. The solvent was removed by reduced-pressure rotary evaporation. Methanol and a small amount of water was added to the crude mixture, the vessel was heated, and the product was isolated as a white powder after filtration of the cooled solution (6.18 g, 95%)

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta$ ): 10.00-8.00 (m, 12H, NH), 3.61(br s, 32H), 1.55 (br s, 16H), 1.41 (br s, 32H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): = 168.83, 168.40, 168.11, 167.64, 167.30, 164.64, 164.37, 43.40, 25.45, 24.48; MS (MALDI-TOF) exact mass calcd for  $\text{C}_{61}\text{H}_{92}\text{ClN}_{41}$  = 1433.81; found 1434.62  $[\text{M}+\text{H}]^+$ .



**Dendron 6.** In a pressure flask was placed dendron 5 (4.00 g, 27.9 mmol) with 50 mL of THF. Anhydrous hydrazine (0.44 mL, 13.9 mmol) was added to the solution and the vessel was sealed. The reaction was heated at 80 °C for 24 h. Methanol and  $\text{H}_2\text{O}$  were added to the reaction and the product precipitated. The white powder was collected by filtration and dried. (3.83, 96%)

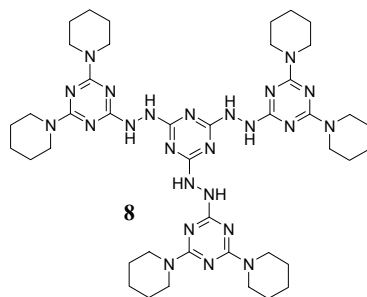
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 9.00-8.00 (m, 13H, *NH*), 4.00 (br s, 2H, *NH*), 3.61 (br s, 32H), 1.55 (br s, 16H), 1.41 (br s, 32H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 168.02, 167.32, 164.60, 164.35, 43.40, 25.45, 24.48; MS (MALDI-TOF) exact mass calcd for  $\text{C}_{61}\text{H}_{95}\text{N}_{43}$  = 1429.88; found 1430.76  $[\text{M}+\text{H}]^+$ .



**Dendrimer 7 (G1-dimer).** Intermediate **1** (1.00 g, 3.61 mmol) and intermediate **2** (1.02 g, 3.62) were dissolved in 30 mL of THF in a pressure flask. The vessel was closed and heated in an oil bath at 105 °C for 36 h. The solution was cooled to room temperature before opening the flask, and then transferred to a round bottom flask. The solvent was removed by reduced-pressure rotary evaporation. To purify the crude reaction a recrystallization from hot methanol was attempted. A large portion of the material would not dissolve in the hot methanol, and this was collected by conducting a hot filtration. The white powder collected was the desired product, showing a single  $[\text{M}+\text{H}]^+$  peak by ESI-TOF mass spectral analysis and a single spot by TLC (1.24 g, 66%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 6.73 (s, 1H, *NH*) 3.68 (m, 8H), 1.61 (m, 4H), 1.51 (m, 8H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 167.98, 164.94, 44.08, 25.71, 24.92; MS (ESI-TOF) exact mass calcd for  $\text{C}_{26}\text{H}_{42}\text{N}_{12}$  = 522.37; found 523.37  $[\text{M}+\text{H}]^+$ .





**Dendrimer 8 (G1-trimer).** Intermediate **1** (1.50 g, 5.41 mmol) was dissolved in 30 mL THF in a pressure flask. The solution was cooled in an ice bath, followed by addition of cyanuric chloride (332 mg, 1.80 mmol) and DIEA (1 mL, 5.75 mmol), and then sealed. The flask was removed from the ice bath and warmed to room temperature while stirring. The flask was then heated in an oil bath at 105 °C for 36 h. The solution was cooled to room temperature before opening the flask, and then transferred to a round bottom flask. The solvent was removed by reduced-pressure rotary evaporation. Hot methanol was added to the crude mixture (~30 mL), and some material dissolved. A hot filtration of the solution resulted in the isolation of a white powder, which was the desired product (854 mg, 52%).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 8.00-7.40 (m, 4H, NH), 3.61 (br, 24H), 1.55 (br, 12H), 1.46 (br, 24H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 169-167, 165.00, 44.26, 26.00, 25.24; MS (ESI-TOF) exact mass calcd for  $\text{C}_{42}\text{H}_{66}\text{N}_{24}$  = 906.59; found 907.59  $[\text{M}+\text{H}]^+$ , 454.30  $[\text{M}+2\text{H}]^{2+}$ .

## CHAPTER V

### MELAMINE DENDRIMERS FOR BIOCHEMICAL INVESTIGATIONS

#### 5.1 Introduction

Applications of dendrimers in the field of drug delivery are pursued with the hopes of identifying novel macromolecular constructs for the site-specific delivery of therapeutically relevant drugs. Synthetic polymers are currently being pursued as drug delivery vehicles and polyethylene glycols (PEGs) have found extensive use as solubilizing and protein modification reagents.<sup>227</sup> The appending of PEGs to the surface of a protein increases its circulation time through reduction of proteolytic susceptibility.

For a protein of interest to function as an effective therapeutic agent a balance needs to be struck among specificity, potency, and pharmacokinetic parameters. Glycoproteins are notorious for occurring in multiple glycoforms, and the heterogeneity translates into variable pharmacokinetic properties when administered.<sup>228</sup> Efforts to design polymer-protein constructs have resulted in the synthesis of macromolecules of defined covalent structure. Monodisperse polymers have been attached to monodisperse chemically synthesized therapeutically relevant proteins.<sup>229</sup>

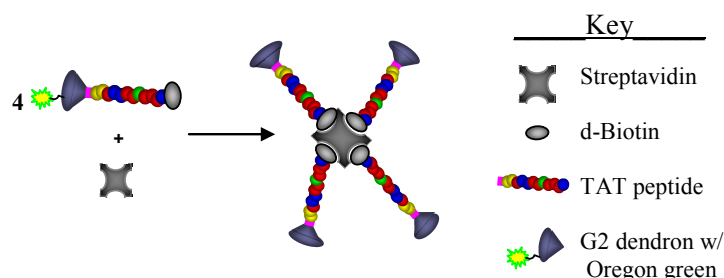
Dendrimer chemistry has the goal of producing monomolecular compounds, but the endeavor tends to be labor intensive. While advances in methods to speed the synthesis of dendrimers have appeared (Chapter II) considerable effort is still expended in the construction of large constructs. Applicability of dendrimers as drug delivery vehicles relies on construction of molecules exceeding ~40kDa to take advantage of the enhanced-permeability-retention (EPR) effect.<sup>230</sup> The EPR effect stems from the ill developed vasculature and lymphatic system supplying a rapidly growing tumor. The vessels supplying the tumor tend to be leaky, allowing the passage of large molecules through the vascular walls. The lymphatic system is under developed, and as such large molecules tend to pool in tumors, as routes for their removal are limited. Efforts to construct dendrimers large enough to take advantage of the EPR effect have relied on the attachment of large PEG groups to a smaller dendrimer.<sup>231</sup> The attachment of polydisperse PEGs to a dendrimer negates the monomolecular nature of the dendrimer.

A novel and efficient method for the rapid construction of macromolecular assemblies which exceed the minimum threshold for EPR was designed, capitalizing on the synthesis of multifunctional dendrimers with chemoselective reactivity and specific protein ligand interactions.

## 5.2 Rationale

For rapid access to macromolecules of large molecular mass nature was utilized to synthesize the major portion of the construct. Streptavidin is a homotetrameric protein of 60 kDa which shows a remarkably high affinity for biotin of  $10^{14} \text{ M}^{-1}$ . Streptavidin can bind up to four biotins, which also serve to stabilize the tetramer. A dendrimer-peptide-biotin conjugate was constructed for the biotin mediated assembly of a protein-dendrimer hybrid. The protein provides the molecular weight while the dendron provides the opportunity to affix molecules of interest, such as a florescent label or drug.

The project was conducted in collaboration with Ms. Megan McLean of the Simanek research group, who synthesized a TAT peptide sequence on the solid support containing a biotin at the C-terminus and an isonipecotic (INP) acid located at the N-terminus. The TAT sequence is an arginine-rich protein transduction domain (PTD) derived from HIV-1. TAT sequences show great efficacy in facilitating cellular uptake of attached cargos; for example antibodies,<sup>232</sup> polymers,<sup>233</sup> nanoparticles,<sup>234</sup> and proteins<sup>235</sup> all exhibit increased cellular uptake with a pendant TAT peptide. The C-terminal biotin was included for the molecular recognition and assembly of the construct around the streptavidin core. Isonipecotic acid, containing a nucleophilic secondary amine, was incorporated for attachment to a melamine dendrimer containing a monochlorotriazine.<sup>207</sup> The resulting construct (Figure 5.1), termed a megamer-biotin-streptavidin (MBS) dendrimer hybrid, results in a monomolecular protein-biotin-peptide-dendrimer construct.

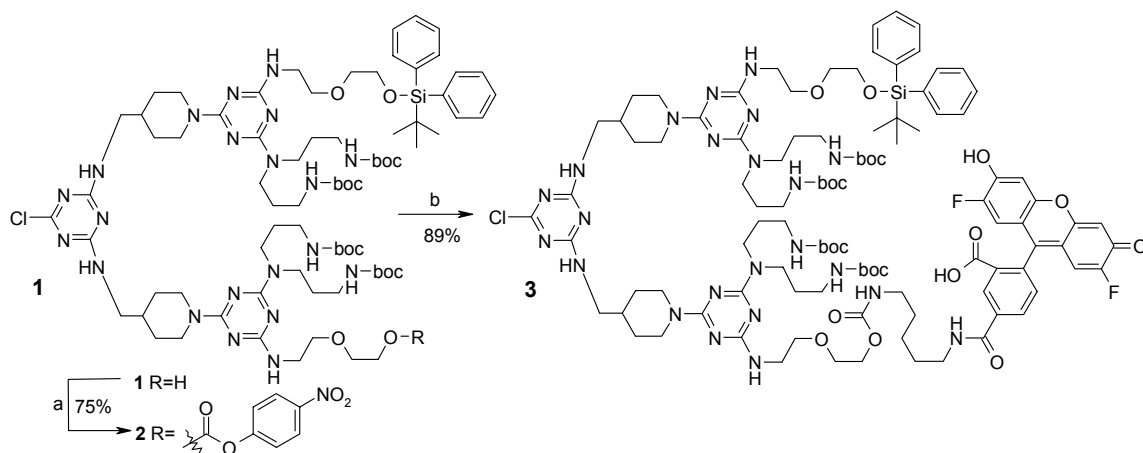


**Figure 5.1.** Schematic representation of the MBS dendrimer hybrid. Picture modified and used with the permission of Megan McLean.

The dendrimer was rapidly synthesized, presenting a single fluorescent tag, a protected hydroxyl for attachment of a molecule of interest, as well as four BOC-protected amines. The dendron also contained a monochlorotriazine used in the coupling of the dendron to the INP terminated peptide.

### 5.3 Materials and Methods

Using heterofunctional building blocks readily accessible through a convergent approach, the G2 dendron **1** containing a free hydroxyl group, a *tert*-butyldiphenylsilyl (TBDPS) protected alcohol and four BOC-protected amines was constructed. The synthesis of **1** started with the addition of a G1 triazine monomer containing a free primary amine, a TBDPS protected alcohol, and two BOC-protected amines (intermediate **7**, Chapter III) to a solution containing one equivalent of cyanuric chloride at 0 °C. The reaction was monitored by TLC, and following consumption of the starting material one equivalent of the second G1 dendron containing a free primary amine, a free alcohol and two BOC-protected amines (intermediate **6**, Chapter III) was added at room temperature. The resulting monochlorotriazine, **1**, was isolated using silica gel chromatography.



**Scheme 5.1.** Synthesis of dendron-Oregon green construct. a) *p*-nitrophenylchloroformate, DMAP, TEA, THF, rt, 90 m; OGC, pyridine, DMF, rt, 4h . DMAP = 4-dimethylaminopyridine; TEA = triethylamine; OGC = Oregon green 488 cadaverine from Molecular Probes #O-10465.

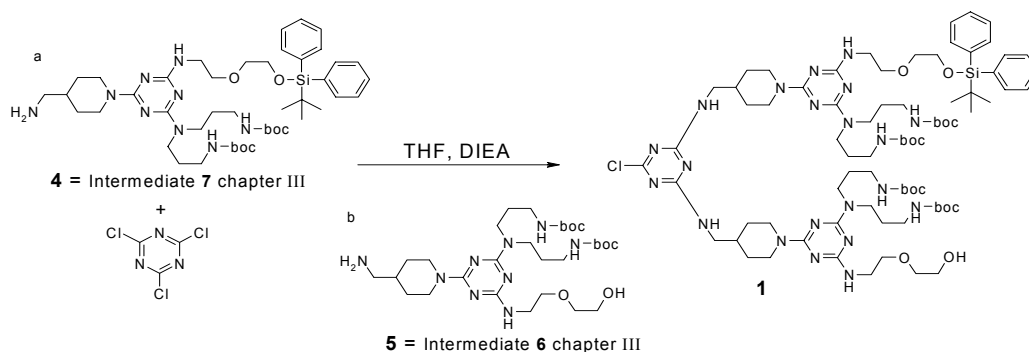
Reaction of the free alcohol of **3** with *p*-nitrophenylchloroformate gave the activated carbonate intermediate **4** (Scheme 5.1). Intermediate **4** was coupled to the fluorescent fluoresceine analog Oregon Green, containing a cadaverine amine linker. The resulting fluorescent labeled dendrimer was purified using silica gel chromatography and isolated in 89% yield, giving 19.0 mg of material.

Attachment of dendron **3** to the INP terminated peptide constructed on the solid support through substitution of the monochlorotriazine using the free secondary amine was accomplished and the products characterized by Ms. McLean. Further characterization and studies surrounding the assembly of the MBS dendrimer hybrid were conducted by Ms. McLean also.

## 5.4 Conclusions

Tailored dendrimers offer potential tools for investigation in biological chemistry. The incorporation of multiple functional groups at the terminal position of dendrimers provide sites for the incorporation of various molecules for studies of interest.

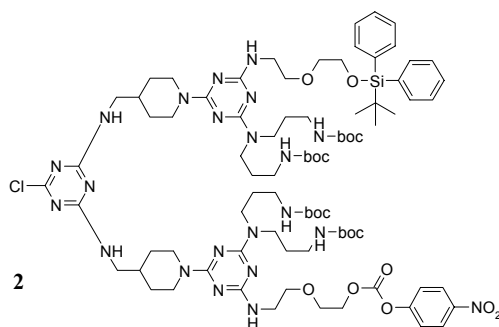
## 5.5 Experimental: Preparation and Characterization



**Dendron 1.** In a round bottom flask with 40 mL of THF was placed intermediate **4** (4.45 g, 5.15 mmol). The solution was cooled in an ice bath, and while stirring cyanuric chloride (950 mg, 5.15 mmol) was added followed by addition of Hunig's base (DIEA, diisopropylethylamine) (2.5 mL, 14.4 mmol). The solution was stirred and warmed to room temperature over 4 h. Intermediate **5** (3.22, 5.15 mmol) was added to the solution and left at room temperature for 24

h. The solvent was removed by reduced-pressure rotary evaporation, and the residue purified by silica gel chromatography using 8:2 EtOAc:Hexanes to 100% EtOAc as the eluant. The product was a white foam upon drying (8.28 g, 89%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, δ): 7.53 (m, 4H), 7.24 (m, 6H), 4.56 (br, 4H), 3.67 (m, 2H), 3.57 (m, 2H), 3.50-3.30 (br m, 18H), 3.18 (m, 4H), 2.91 (br, 8H), 2.62.70-2.60 (br m, 4H), 1.75-1.50 (br m, 13H), 1.29 (s, 36H), 1.08 (m, 4H), 0.91 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, δ): 167.19, 165.40, 164.93, 164.06, 155.93, 135.04, 133.01, 129.16, 127.17, 78.75, 71.83, 69.74, 63.01, 60.91, 46.01, 42.81, 42.11, 40.07, 36.95, 36.42, 29.32, 28.07, 27.41, 26.44, 18.83; MS (ESI-TOF) exact mass calcd for C<sub>77</sub>H<sub>126</sub>ClN<sub>21</sub>O<sub>12</sub>Si = 1599.94; found 1600.93 [M+H]<sup>+</sup>, 800.98 [M+2H]<sup>2+</sup>.



**Dendron 2.** In a round bottom flask with 10 mL THF dendron **1** (400 mg, 0.250 mmol) was dissolved. In a vial *p*-nitrophenylchloroformate (*p*-NPCF) (75.5 mg, 0.375 mmol) was added followed by 5 mL of THF, followed by addition of 0.1 mL of triethylamine (0.717 mmol). The solution containing the *p*-NPCF was transferred to the flask containing dendron **1**. The solution was stirred at room temperature for 1 h. The solvent was removed by reduced-pressure rotary evaporation, and the crude product purified by silica gel chromatography using 8:2 EtOAc:Hexanes → 100% EtOAc as the eluant. The product was a white foam upon drying (331 mg, 75%).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, δ): 168.56, 166.16, 156.23, 152.71, 135.81, 133.84, 129.85, 127.88, 126.36, 125.54, 122.01, 115.88, 79.25, 72.49, 70.34, 68.61, 63.61, 46.65, 43.27, 42.46, 40.86, 37.09, 30.06, 28.73, 28.03, 27.05, 19.41; MS (MALDI-TOF) exact mass calcd for C<sub>84</sub>H<sub>129</sub>ClIn<sub>22</sub>O<sub>16</sub>Si = 1764.94; found 1766.53 [M+H]<sup>+</sup>.

MS (MALDI-TOF) average mass calcd for  $\text{C}_{104}\text{H}_{146}\text{ClF}_2\text{N}_{23}\text{O}_{19}\text{Si} = 2124.00$ ; found 2125.20  $[\text{M}+\text{H}]^+$ .

## CHAPTER VI

### CONCLUSION

Tremendous advances have occurred in the field of polymer science in the last century. It has developed from an ill defined industrial pursuit to a well defined scientific discipline. The development of dendrimer chemistry was a natural extension in polymer chemist's pursuit of novel architectures and novel materials. Currently minimal applications for dendrimers exist, however the field has remained vibrant since its inception through the conduction of basic research into the novel properties of dendrimers. Dendrimers are a solution looking for a problem.

Melamine dendrimers fit a unique niche in the dendrimer spectrum. While their utility remains to be demonstrated, along with other types of dendrimers in the field, current possibilities for their application exist. However, the most important information gleaned from these studies relates to the identification methods for access to highly functionalized materials.

Examples describing control over the composition of the interior linkage groups of melamine dendrimers were discussed in Chapter I. Multiple unique linking groups were incorporated in an efficient manner. The construction of a dendrimer through the convergent approach with multiple reactions conducted in a single pot demonstrates the ability to access designed dendrimers. Latent functionality is left unprotected through the entire dendrimer synthesis, providing the possibility for further post-synthetic functionalization of the material. There was no need for functional group interconversions, all the functionality necessary for the dendrimer construction is present using cyanuric chloride and the selected amine. Cyanuric chloride as a tri-electrophilic core provides controlled substitution at each position in a temperature dependent manner. Monochlorotriazines show chemoselective reactivity with amine nucleophiles, with secondary amines being much more reactive than primary and primary amines more reactive than benzylic and aromatic amines respectively.

Examples were described using methods to construct dendrimers containing multiple surface functionalities. The incorporation of multiple functional groups at the dendrimer periphery provides a macromolecular scaffold for the attachment of molecules of interest. The ability to tailor the functionality at the terminal groups offers opportunities to post-synthetically modify the dendrimers to produce a library of materials for a desired application or study. The



incorporation of such a scaffold on a solid support would greatly accelerate the steps required for post-synthetic manipulation of the terminal groups, providing a more rapid route to access multifunctional dendrimers.

Combination of the techniques employed in Chapters I and II could be combined to produce a dendrimer with unique functionality located at each branch point and at each surface group. The methods would be amendable to the construction of a macromolecule where the exact atomic connectivity is known, and the compound is truly monomolecular. The imagination could lead one to see the analogy between such dendrimers and proteins. The functional groups of proteins are located with precise atomic connectivity, with multiple functional groups per protein, the amide linkage being the common building block. Proteins, through intramolecular interactions, fold to adopt a well defined structure often of a globular nature. In a melamine dendrimer multiple functionality can be placed within the dendrimer interior and at the surface with precise atomic placement, the common structural element being the triazine ring. Dendrimers of large enough generations also tend to assume a globular structure. While melamine dendrimers are a long way from offering such a fanciful or functional material as proteins now do, they offer a fertile field for the imagination to wander and ponder on such potential structures.

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## **APPENDIX A**

### **REFERENCES, FIGURES AND SCHEMES RELEVANT TO CHAPTER I**

## TRIAZINE DENDRIMER SYNTHESES

Group	Size <sup>‡</sup>	Method of Synthesis	Triazine location	C/D <sup>†</sup>	Journal/Patent	Date submitted	Page #
Niederhauser	D2	Cycloaddition/cyanoethylation	Branching	D	Patent <sup>1</sup>	Jan. 18, 1950	118
Maciejewski	D2	Cycloaddition/cyanoethylation	Branching	D	Patent <sup>2</sup>	Aug. 31, 1994	118
Keana	D2	Cl displacement of CC by aryl N	Branching	D	Patent <sup>3</sup>	Sept. 29, 1994	119
Bauer	G1	Cl displacement of CC by amines	Branching	C/D	Patent <sup>4</sup>	Aug. 8, 1995	119-120
Gluzman	G1	Cl displacement of CC by aryl N	Branching	C/D	Patent <sup>5</sup>	Jan. 27, 1997	120
Fréchet	G4, D4	Cl displacement of CC/cyclization of biuret	Core	C	<i>Poly Mat. Sci. Eng.</i> <sup>6</sup>	1997	121
Kraus	G1	Cl displacement of CC by alkoxy/silyloxy	Branching	C	<i>J. Org. Chem.</i> <sup>7</sup>	Feb. 10, 1998	122
Ellestad	G1	Cl displacement of CC by aryl N	Branching	C/D	<i>J. Med. Chem.</i> <sup>8</sup>	Apr. 20, 1998	120
Maciejewski	D2	Cycloaddition/cyanoethylation	Branching	D	<i>J. Macromol. Sci., Pure Appl. Chem.</i> <sup>9</sup>	June 24, 1999	118
Burn	G1	Cl displacement of CC by alkyl/aryl O	Branching	C	<i>J. Mater. Chem.</i> <sup>10</sup>	Nov. 5, 1999	122
Simanek	G3	Cl displacement of CC by alkyl/aryl N	Branching	C/D	<i>Org. Lett.</i> <sup>11</sup>	Jan. 26, 2000	123
Takagi	G2,D3	Cl displacement of CC by aryl N	Branching/ core	C	<i>Kobunshi Ronbunshu</i> <sup>12</sup>	Mar. 22, 2000	123
Takagi	G2	Cl displacement of CC by aryl N/aryl O/N	Branching/ core	C/D	<i>J. Polym. Sci., Part A: Polym. Chem.</i> <sup>13</sup>	Apr. 20, 2000	125
Neuman-Rodekirch	G1	Phenol displacement of TPOT by alkyl N	Branching/ core	D	<i>Proc. ECSOC-4</i> <sup>14</sup>	Aug. 30, 2000	126
Marsh	D2 <sup>*</sup>	Cl displacement of CC by alkyl O/N	Branching	D	<i>Tetrahedron. Lett.</i> <sup>15</sup>	Sept. 6, 2000	127
Simanek	G3	Cl displacement of CC by amines	Branching	C	<i>J. Am. Chem. Soc.</i> <sup>16</sup>	Dec. 1, 2000	128
Dehaen	G2	Cl displacement of CC by aryl O	Core	C	<i>J. Org. Chem.</i> <sup>17</sup>	Dec. 15, 2000	129
Simanek	D5	Cl displacement of CC by amines	Branching/ FP	C	<i>Tetrahedron. Lett.</i> <sup>18</sup>	Mar. 30, 2001	123

<sup>‡</sup> Generation of dendrimer (G#) or dendron (D#).

<sup>†</sup> Convergent or divergent route.

<sup>\*</sup> Synthesis conducted on a solid support



Dehaen	G2, D3	Grignard/Cl displacement by aryl O	Branching/ Core	C	<i>Mater. Sci. Eng., C</i> <sup>19</sup>	Nov. 7, 2001 <sup>∇</sup>	130
Gamez	G1	Cl displacement of CC by aryl O/N	Branching/ core	C	<i>Tetrahedron. Lett.</i> <sup>20</sup>	May 31, 2002	131
Simanek	G3	Cl displacement of CC by amines	Branching	C	<i>Macromolecules</i> <sup>21</sup>	July 12, 2002	132
Simanek	G4	Cl displacement of CC by amines	Branching	C	<i>J. Am. Chem. Soc.</i> <sup>22</sup>	Aug. 15, 2002	133-134
Su	D4*	Cl displacement of CC by amines	Branching	D	<i>Anal. Lett.</i> <sup>23</sup>	Sept. 6, 2002	135
Simanek	D3	Cl displacement of CC by amines	Branching	C	<i>Bioconjugate Chem.</i> <sup>24</sup>	Sept. 25, 2002	136
Simanek	G3	Cl displacement of CC by amines	Branching/ core	C	<i>Supramolecular Chemistry</i> <sup>25</sup>	Nov. 2, 2002	137
Simanek	G3	Cl displacement of CC by amines	Branching	C	<i>Org. Lett.</i> <sup>26</sup>	Jan. 28, 2003	138
Bradley	D3*	Cl displacement of CC by aryl O	Surface	D	<i>Tetrahedron</i> <sup>27</sup>	Feb. 7, 2003	139
Gamez/ Reedijk	G1	Cl displacement of CC by amines	Branching/ core	C	<i>Inorg. Chim. Acta</i> <sup>28</sup>	Feb. 26, 2003	131
Simanek	G3, D3	Cl displacement of CC by amines	Branching	C	<i>Org. Lett.</i> <sup>29</sup>	Jan. 28, 2003	140
Simanek	D3	Cl displacement of CC by amines	Branching	C	<i>Chem. Mater.</i> <sup>30</sup>	Feb. 19, 2003	141
<b>OTHER 'SUGGESTED' TRIAZINE DENDRIMERS</b>							
Meijer	G0	Cyanoethylation/reduction	Core		Patent <sup>31</sup>	Mar. 10, 1994	142
Tanaka	H <sup>§</sup>	Grignard	Branching/ core		Patent <sup>32</sup>	May 9, 1996	142
Viswanathan	G0	Cl displacement of CC by aryl N	Core		<i>Polym. Prepr.</i> <sup>33</sup>	1997	143
Sanders	G1	Ligand chelation to Ru	Core		<i>New J. Chem.</i> <sup>34</sup>	Jan. 11, 1999	142
Fleet	G1	Cl displacement of CC by amines/aryl O	Core		Patent <sup>35</sup>	Mar. 12, 1999	142
Constable/ Housecroft	G0	Cyclotrimerization/Stille coupling to CC	Core		<i>Inorg. Chim. Acta</i> <sup>36</sup>	Aug. 23, 1999	143
Balogh-Nair	G0	Cl displacement of CC by aryl O	Core		<i>Int. J. Mol. Sci.</i> <sup>37</sup>	June 7, 2002	143

\* Generation of dendrimer (G#) or dendron (D#).

† Convergent or divergent route.

\* Synthesis conducted on a solid support

∇ Date Published

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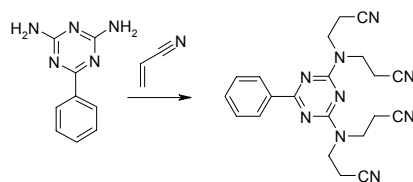
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Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Niederhauser	D2	Cycloaddition/cyanoethylation	Branching	D	Patent	Jan. 18, 1950

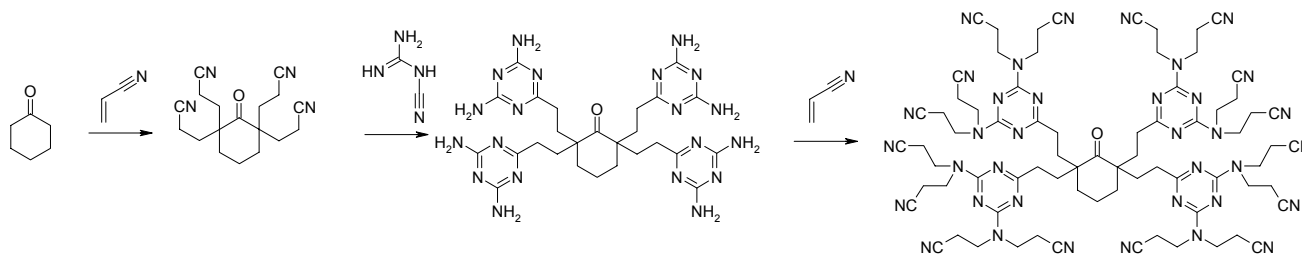
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Maciejewski	D2	Cycloaddition/cyanoethylation	Branching	D	<i>J. Macromol. Sci., Pure Appl. Chem.</i>	June 24, 1999

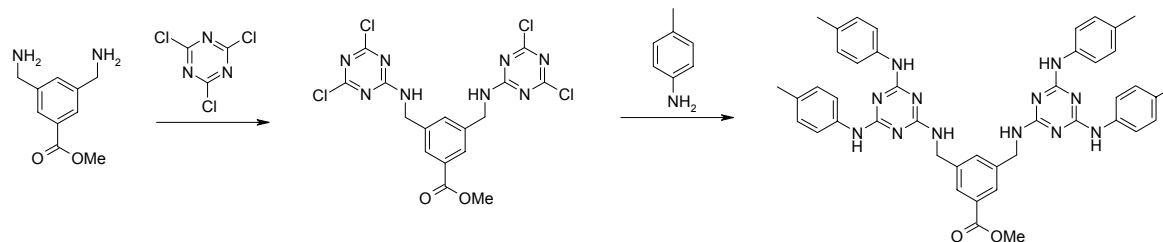
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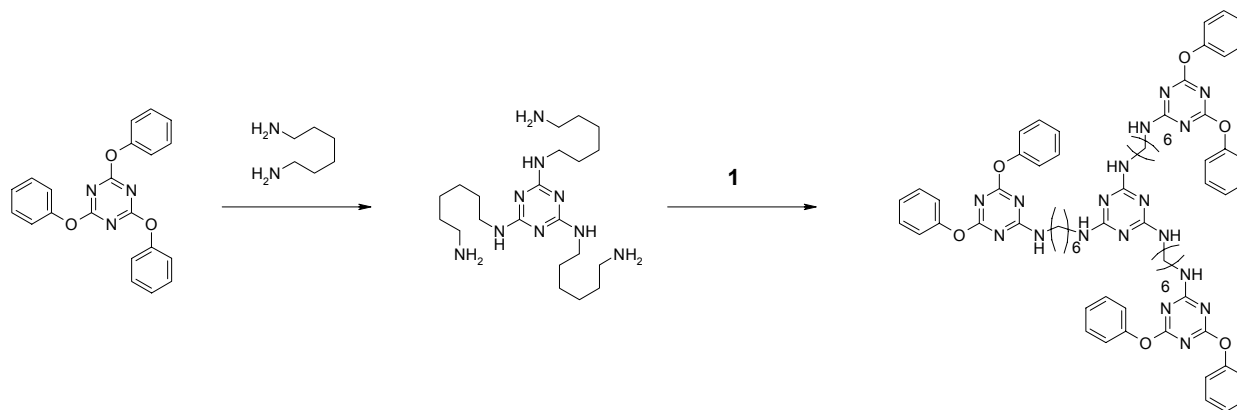
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Keana	D2	Cl displacement of CC by aryl N	Branching	D	Patent	Sept. 29, 1994

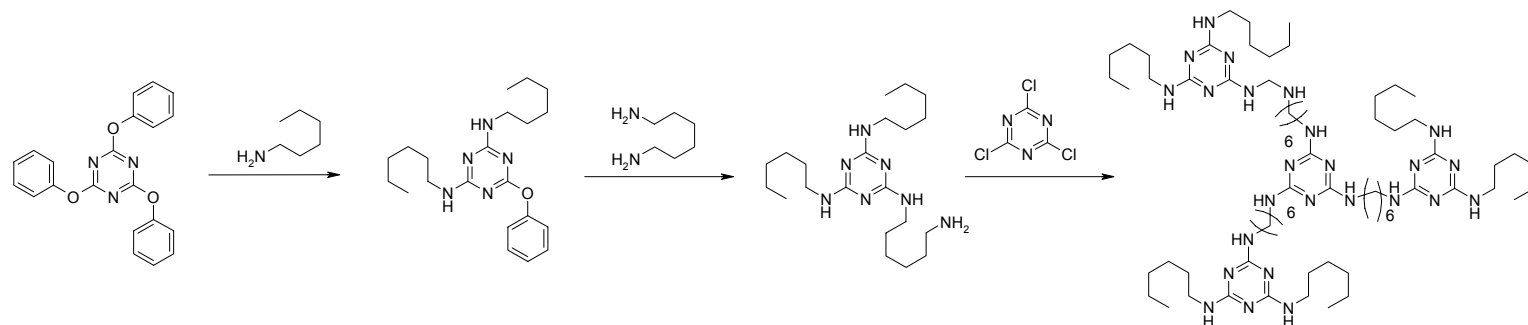
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Bauer	G1	Cl displacement of CC by amines	Branching	C/D	Patent	Aug. 8, 1995

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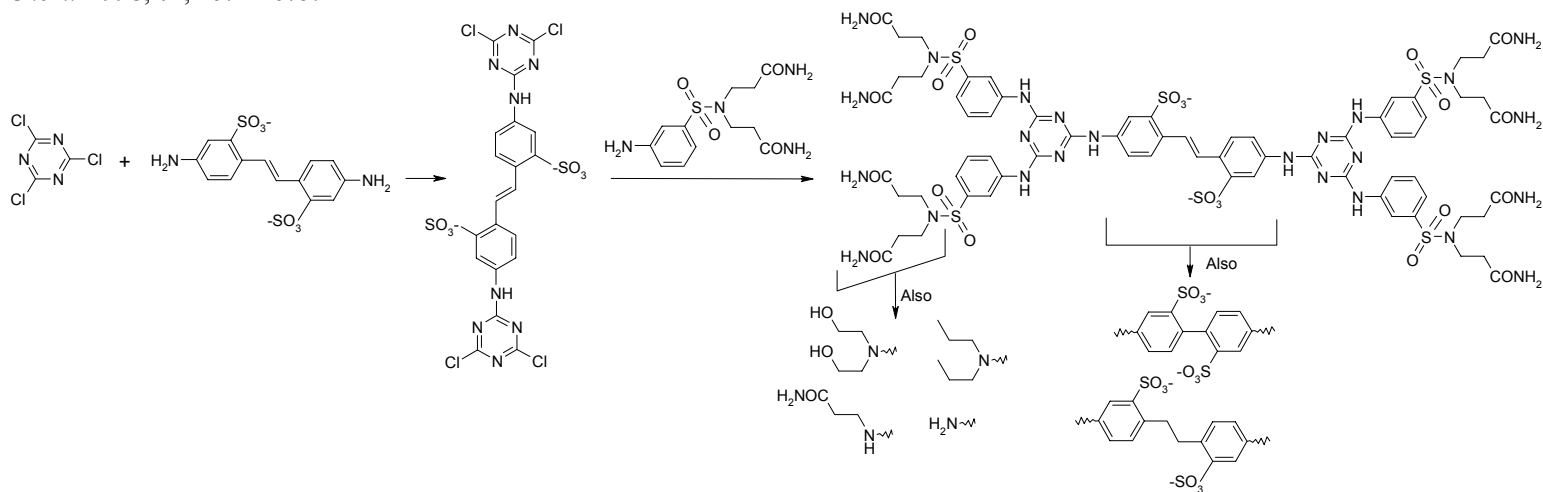




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Gluzman	G1	Cl displacement of CC by aryl N	Branching	C/D	Patent	Jan. 27, 1997
Ellestad	G1	Cl displacement of CC by aryl N	Branching	C/D	<i>J. Med. Chem.</i>	Apr. 20, 1998

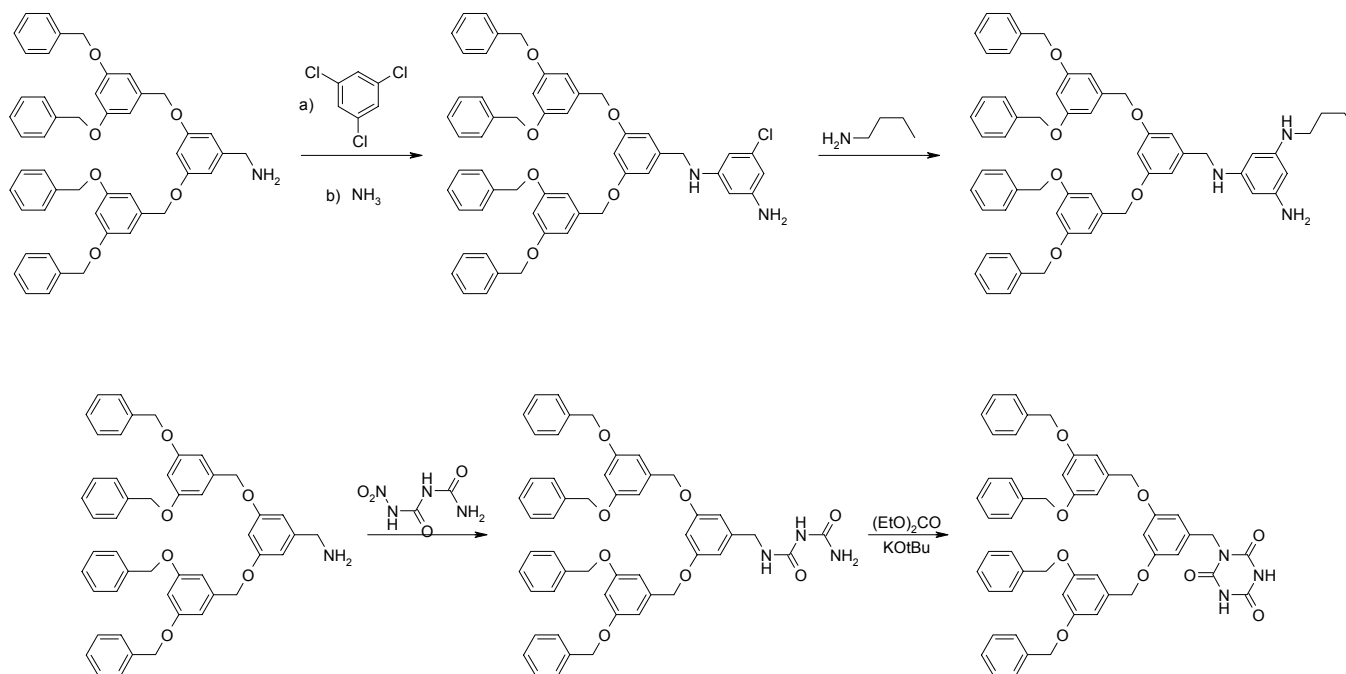
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Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Fréchet	G4, D4	Cl displacement of CC/cyclization of biuret	Core	C	<i>Poly Mat. Sci. Eng.</i>	1997

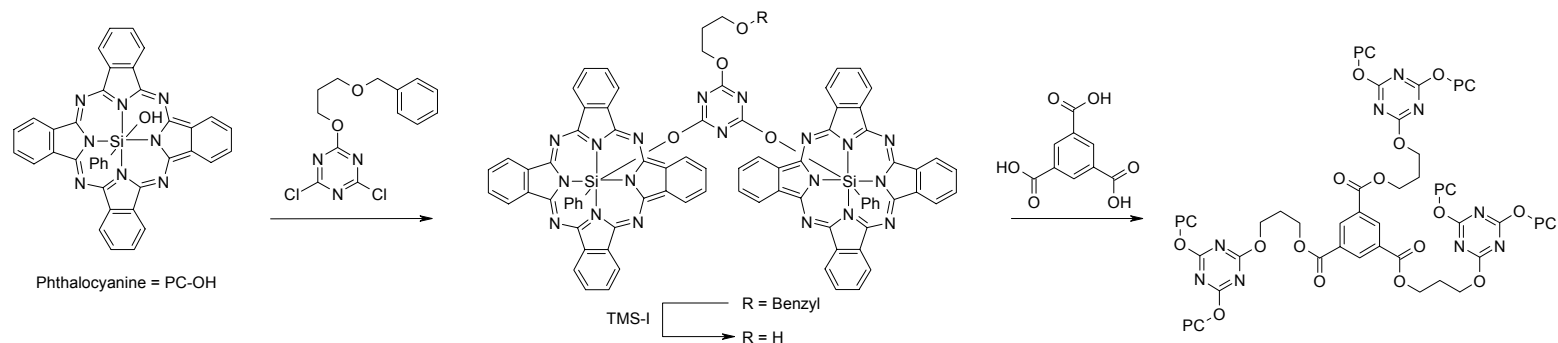
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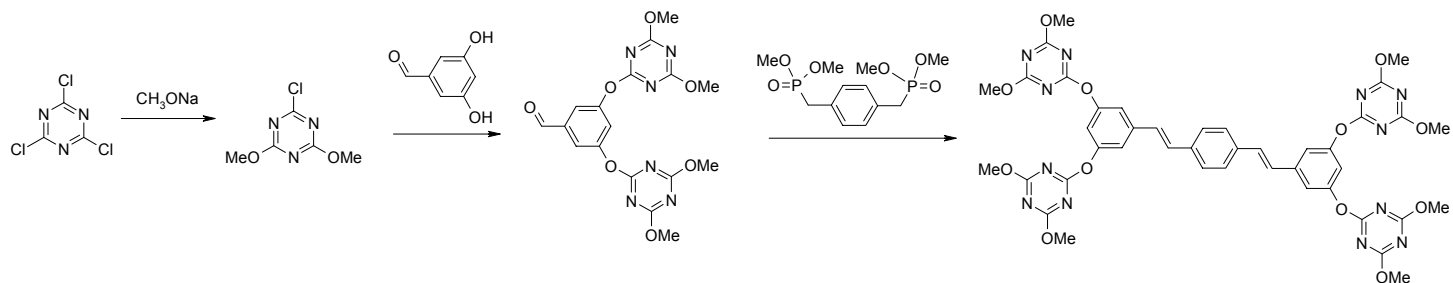
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Kraus	G1	Cl displacement of CC by alkoxy/silyloxy	Branching	C	<i>J. Org. Chem.</i>	Feb. 10, 1998

Kraus, G. A.; Louw, S. V. Synthesis of the first phthalocyanine-containing dendrimer. *J. Org. Chem.* **1998**, *63*, 7520-7521.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Burn	G1	Cl displacement of CC by alkyl/aryl O	Branching	C	<i>J. Mater. Chem.</i>	Nov. 5, 1999

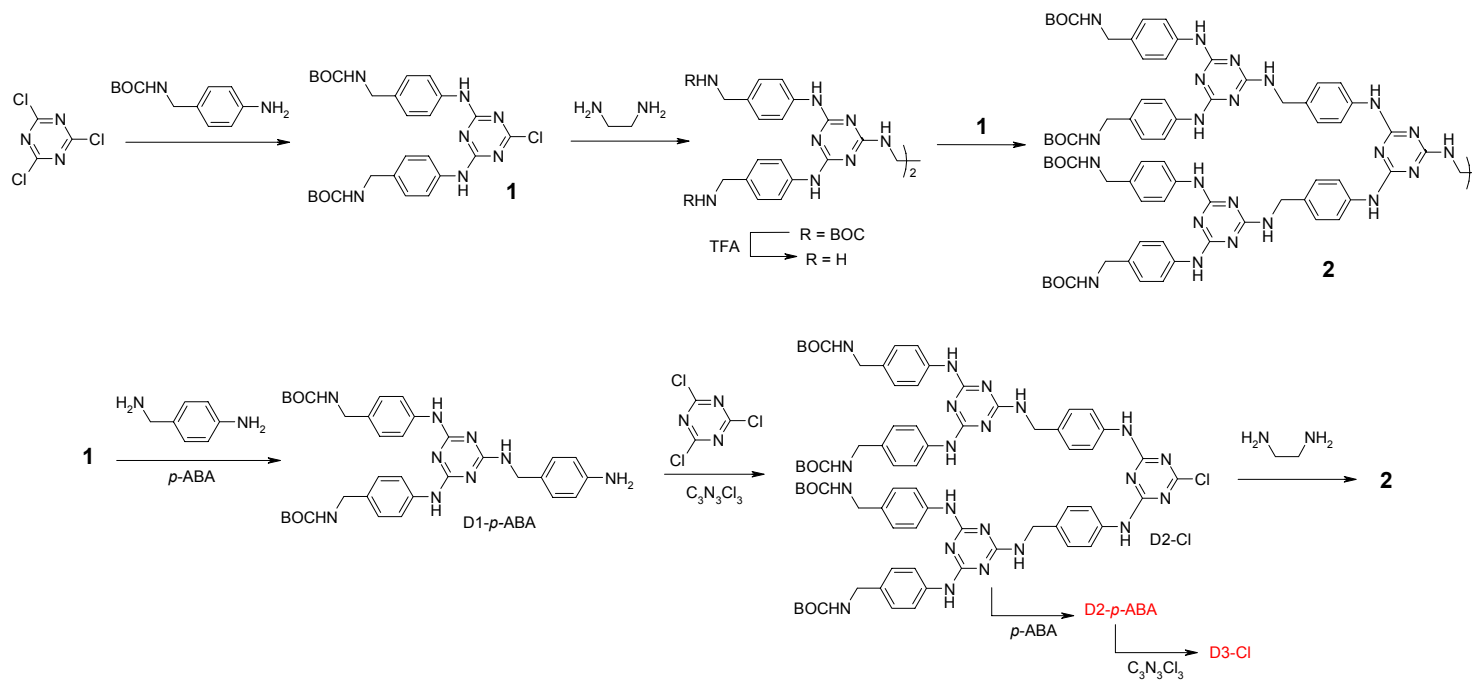
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Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	G3	Cl displacement of CC by alkyl/aryl N	Branching	C/D	<i>Org. Lett.</i>	Jan. 26, 2000
Simanek	D5	Cl displacement of CC by amines	Branching/ FP	C	<i>Tet. Lett.</i>	Mar. 30, 2001

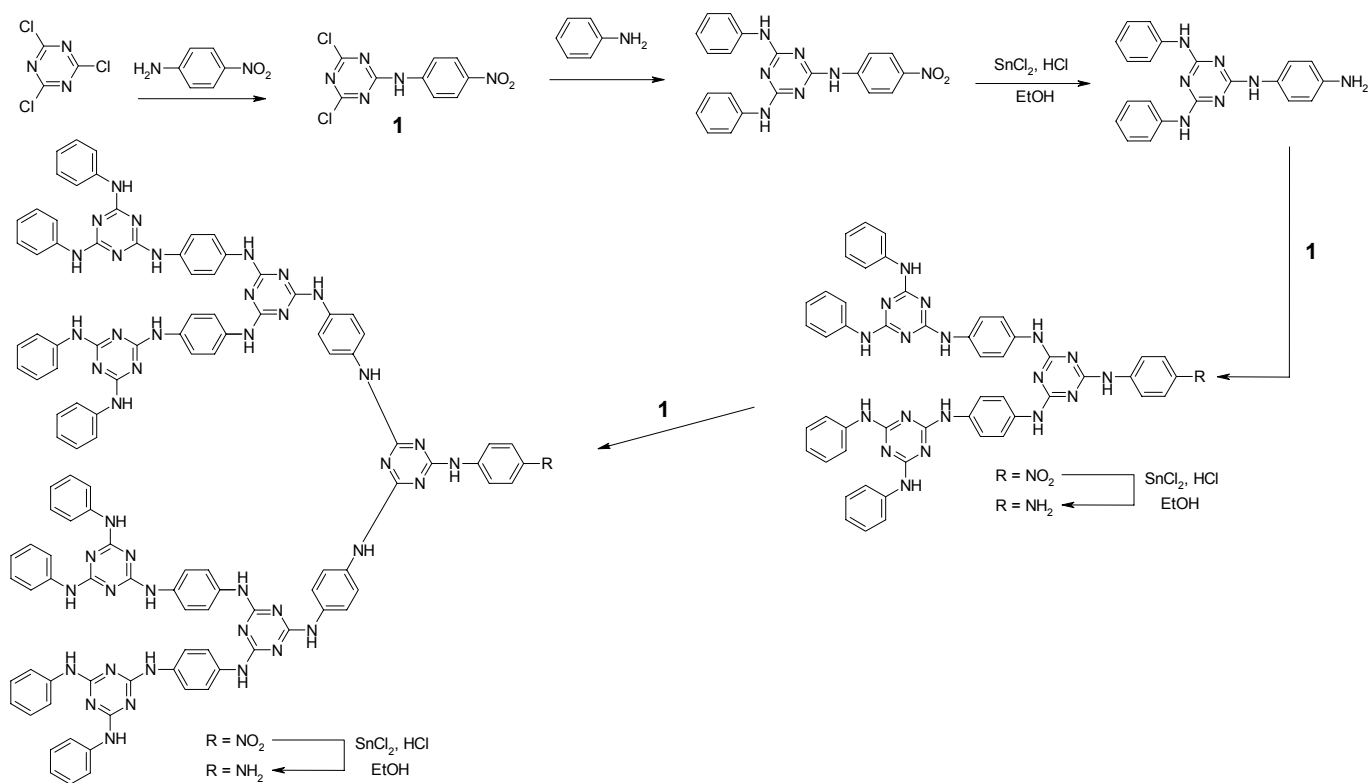
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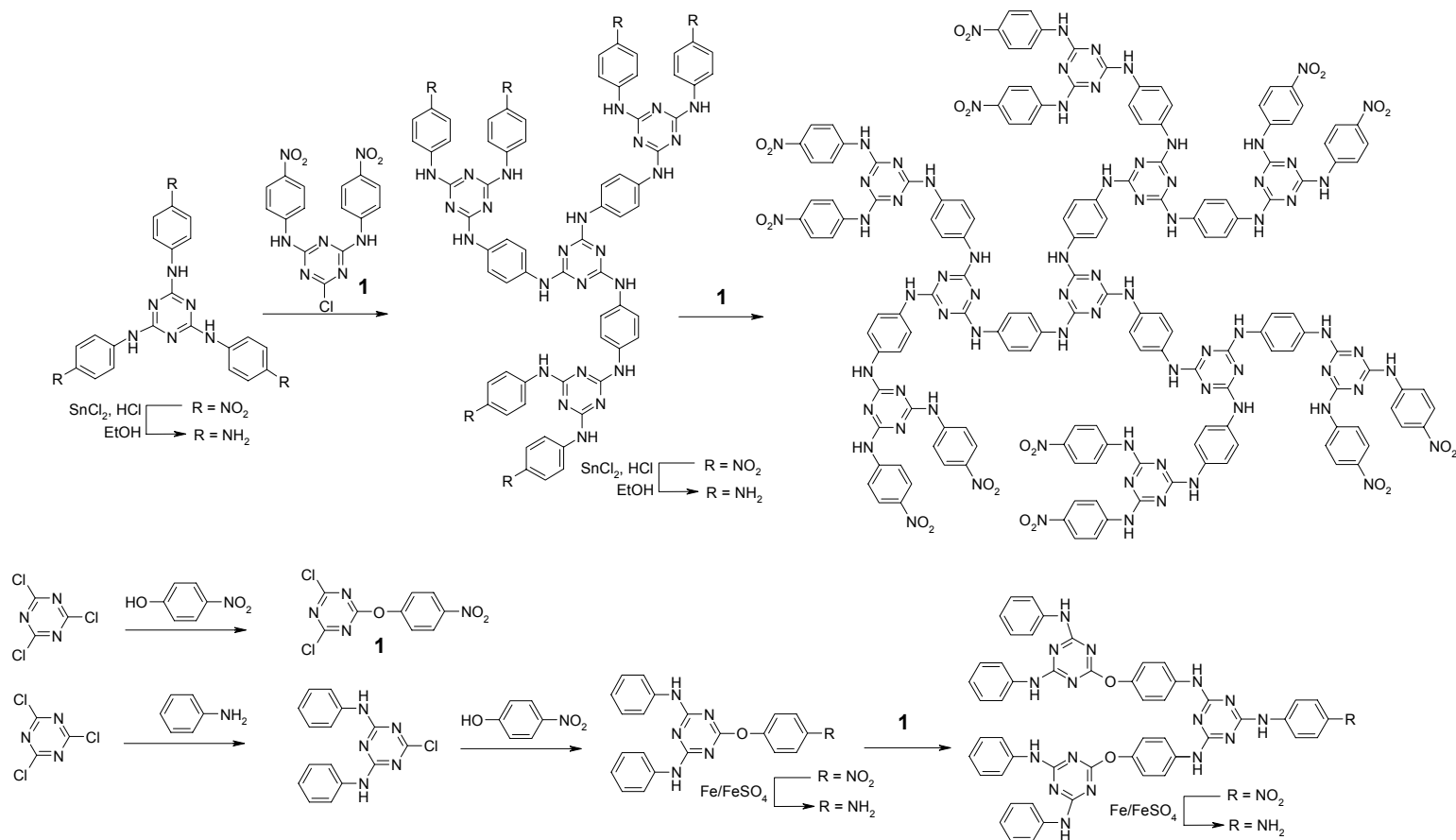
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Takagi	G2,D3	Cl displacement of CC by aryl N	Branching/ core	C	<i>Kobunshi Ronbunshu</i>	Mar. 22, 2000

Takagi, K. Synthesis of triazine dendrimers. *Kobunshi Ronbunshu* **2000**, 57, 646-651.



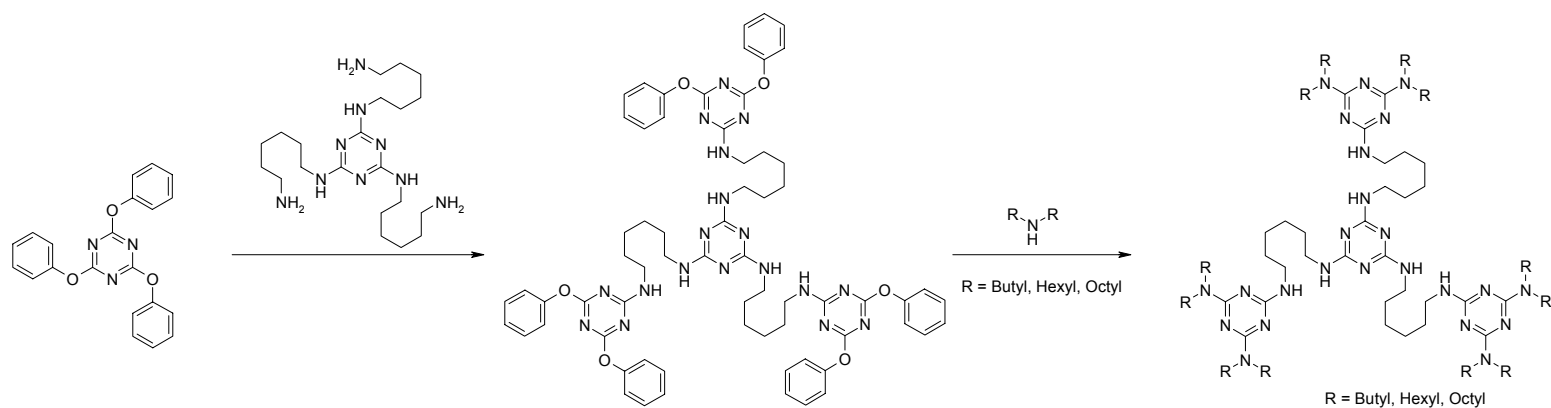
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Takagi	G2	Cl displacement of CC by aryl N/aryl O/N	Branching/ core	C/D	<i>J. Polym. Sci., Part A: Polym. Chem.</i>	Apr. 20, 2000

Takagi, K.; Hattori, T.; Kunsada, H.; Yuki, Y. Triazine dendrimers by divergent and convergent methods. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, 38, 4385-4395.



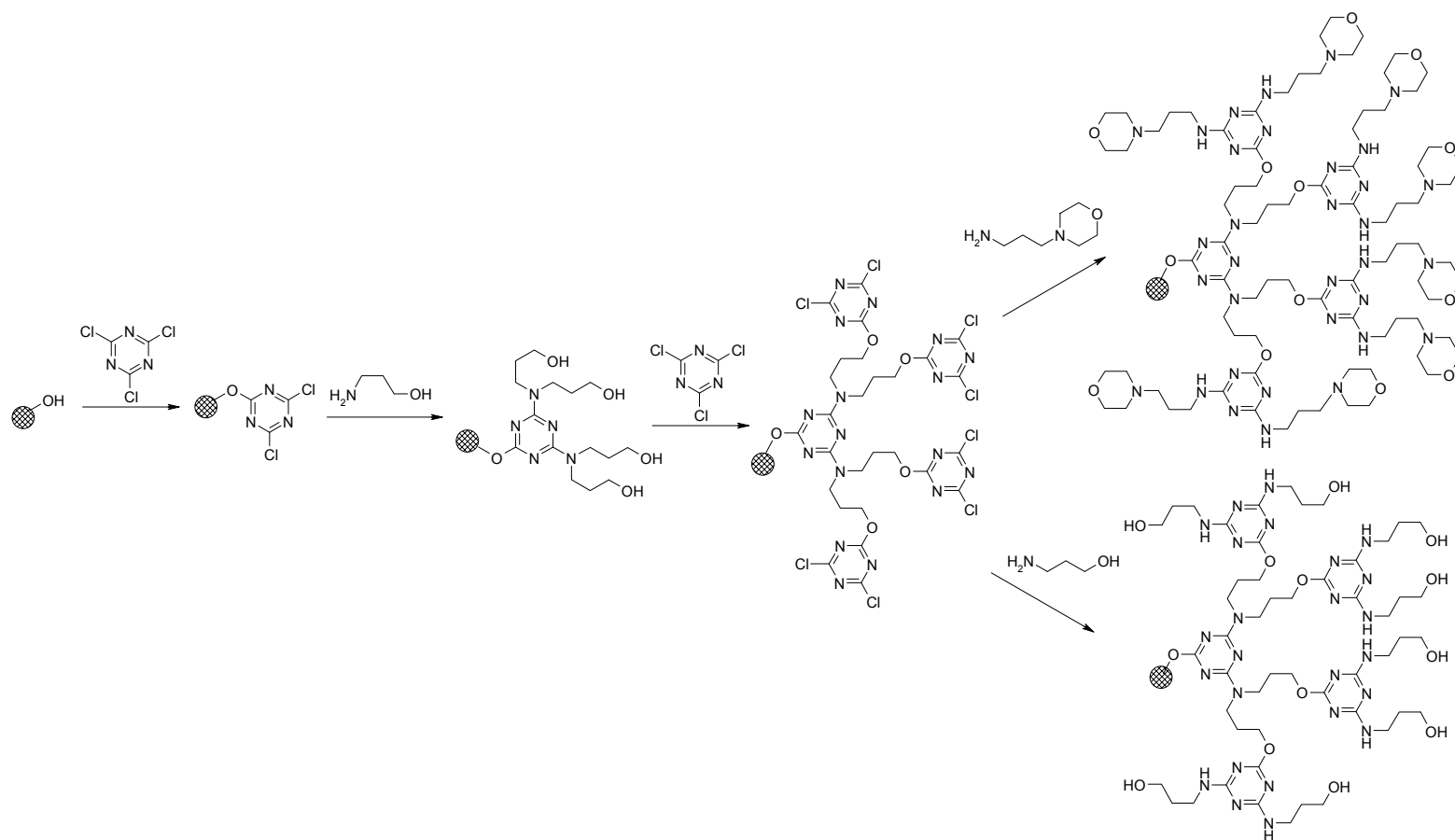
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Neuman-Rodekirch	G1	Phenol displacement of TPOT by alkyl N	Branching/core	D	<i>Proc. ECSOC-4</i>	Aug. 30, 2000

Dreyer, C.; Blume, A.; Bauer, M.; Bauer, J.; Neumann-Rodekirch, J. Triazine based dendrimers. *Proc. ECSOC-3, [and] Proc. ECSOC-4, 2000*, 1196-1213. *Chem. Abstr.* **2000**, 135, 153157.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Marsh	D2	Cl displacement of CC by alkyl O/N	Branching	D	<i>Tetrahedron. Lett.</i>	Sept. 6, 2000

Marsh, A.; Carlisle, S. J.; Smith, S. C. High-loading scavenger resins for combinatorial chemistry. *Tetrahedron Lett.* **2001**, 42, 493-496.



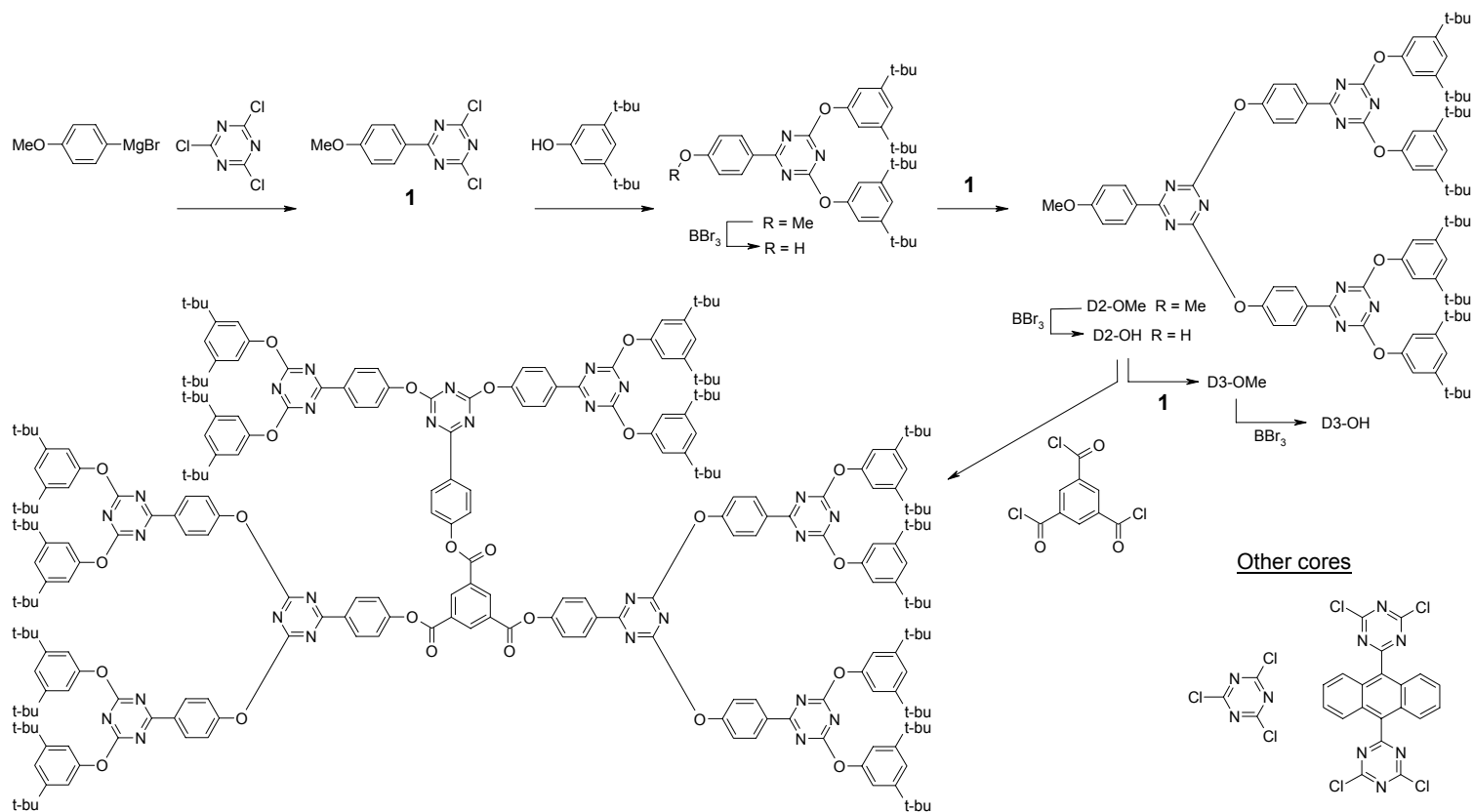






Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Dehaen	G2, D3	Grignard/Cl displacement by aryl O	Branching/ Core	C	<i>Mater. Sci. Eng., C</i>	Nov. 7, 2001

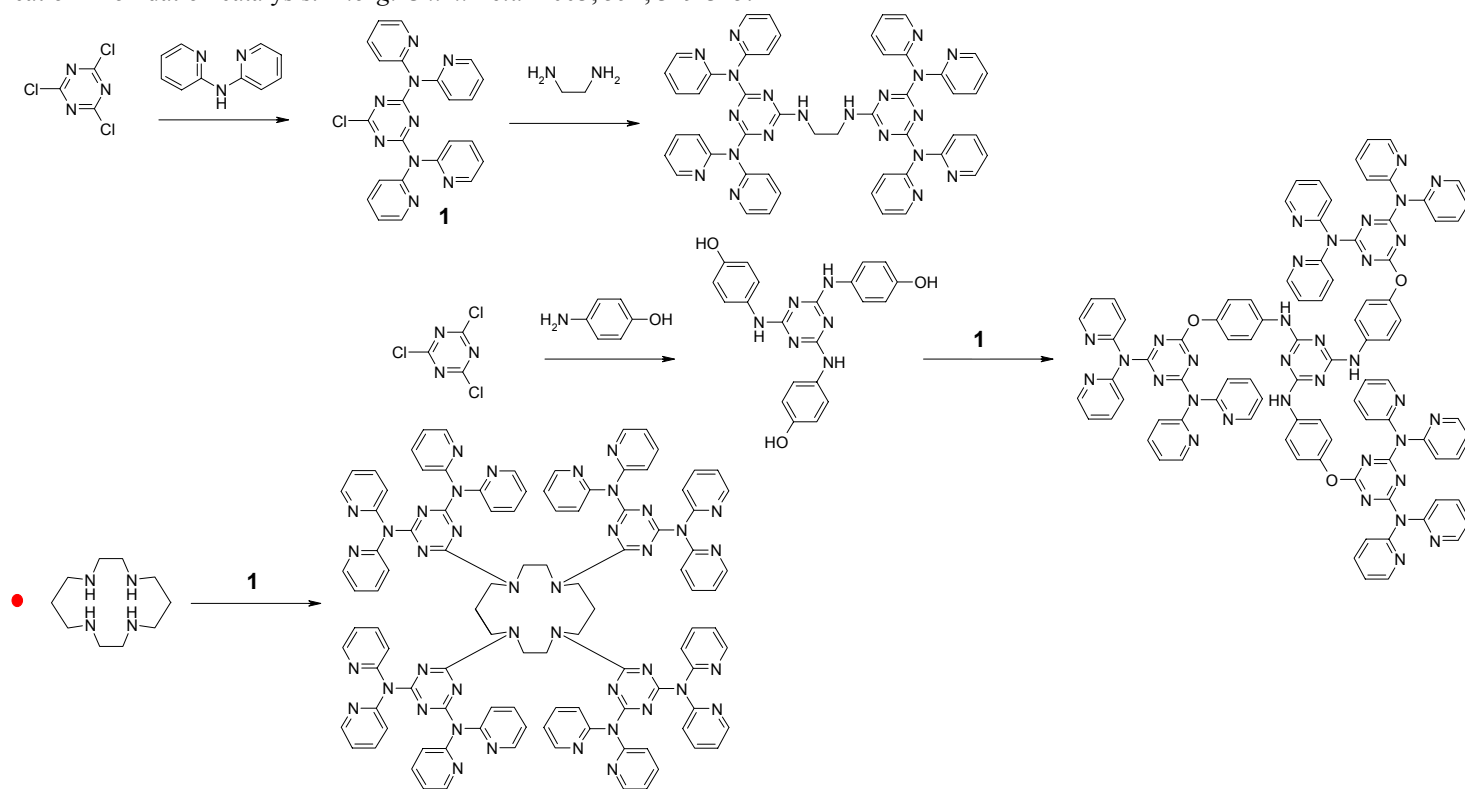
Verheyde, B.; Maes, W.; Dehaen, W. The use of 1,3,5-triazines in dendrimer synthesis. *Mater. Sci. Eng., C* **2001**, 18, 243-245.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Gamez	G1	Cl displacement of CC by aryl O/N	Branching/ core	C	<i>Tetrahedron. Lett.</i>	May 31, 2002
Gamez/Reedijk	G1	Cl displacement of CC by amines	Branching/ core	C	<i>Inorg. Chim. Acta</i>	Feb. 26, 2003

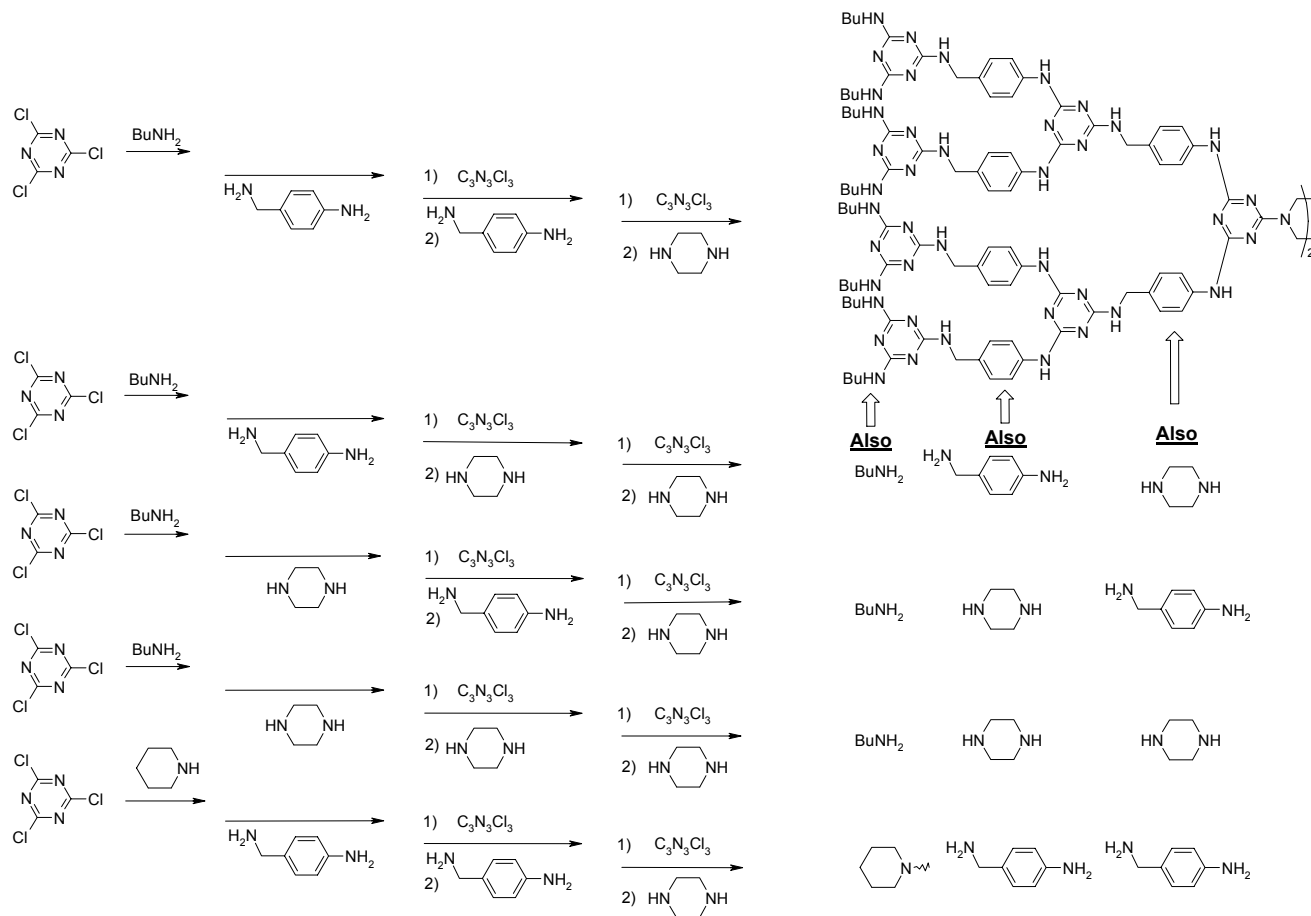
de Hoog, P.; Gamez, P.; Driessen, W. L.; Reedijk, J. New polydentate and polynucleating *N*-donor ligands from amines and 2,4,6-trichloro-1,3,5-triazine. *Tetrahedron. Lett.* **2002**, 43, 6783-6786.

• Gamez, P.; de Hoog, P.; Lutz, M.; Spek, A. L.; Reedijk, J. Coordination compounds from 1,3,5-triazine-derived multi-directional ligands: application in oxidation catalysis. *Inorg. Chim. Acta* **2003**, 351, 319-325.



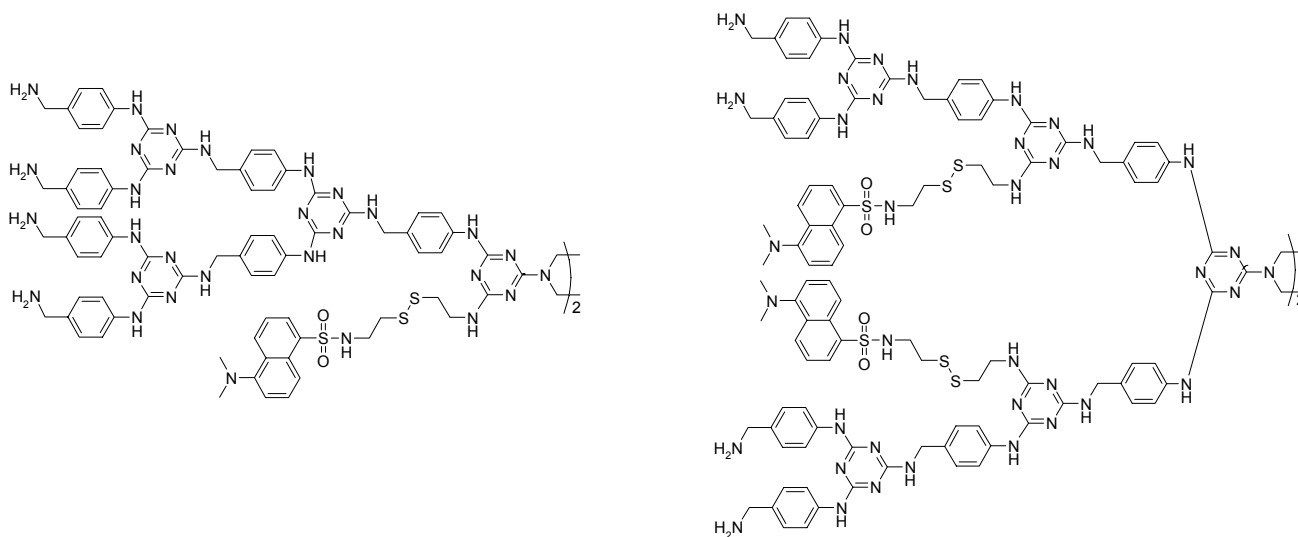
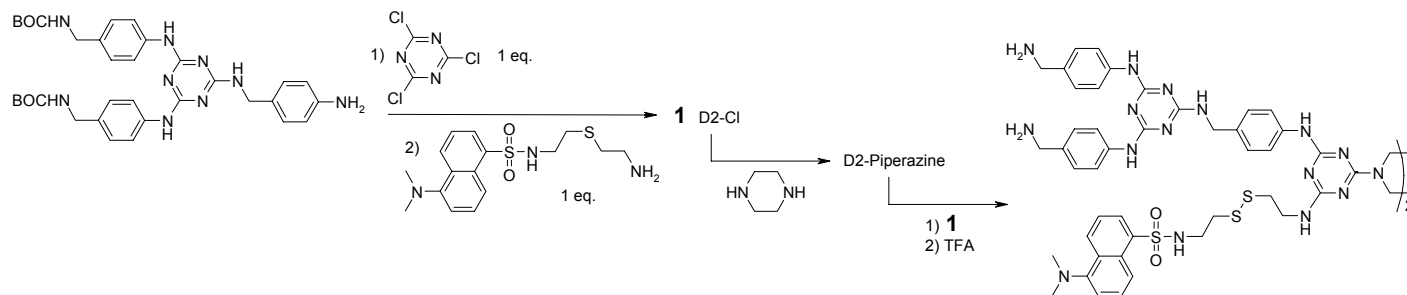
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	G3	Cl displacement of CC by amines	Branching	C	<i>Macromolecules</i>	July 12, 2002

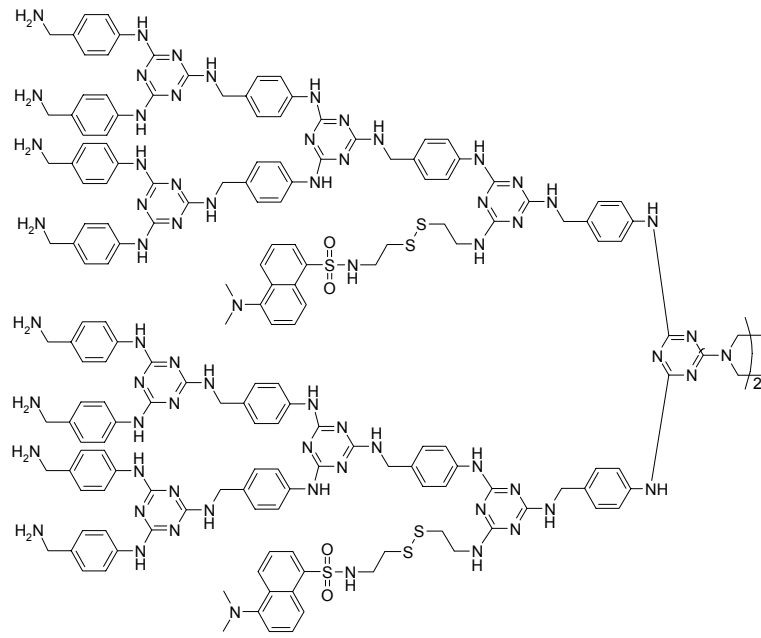
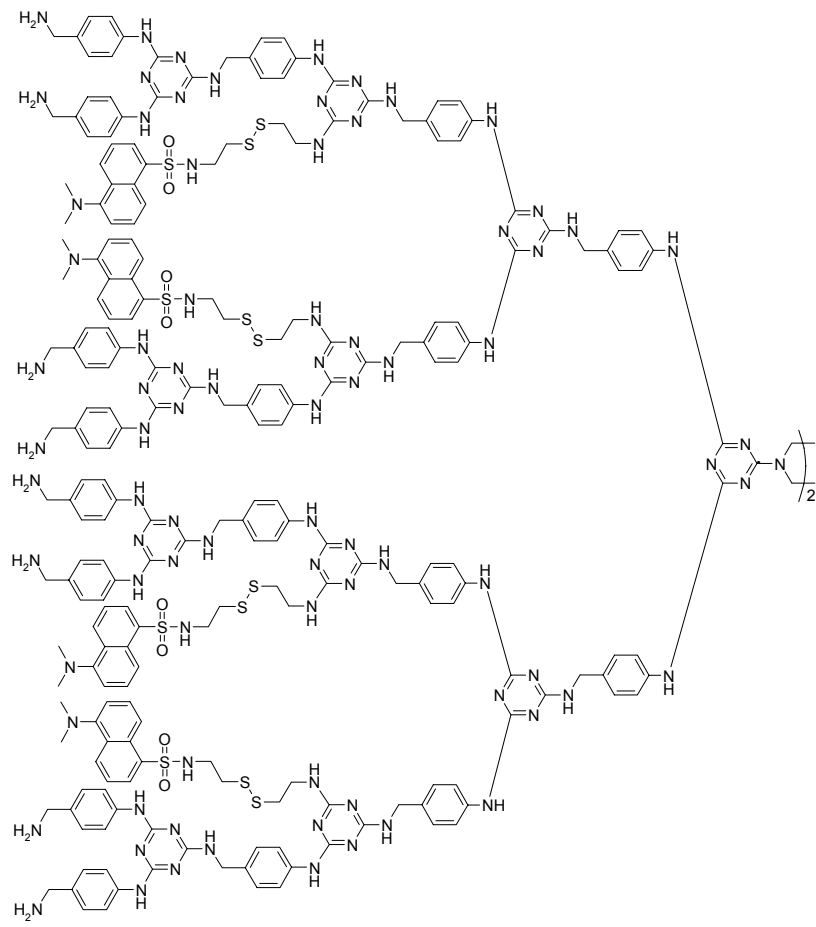
Zhang, W.; Gonzalez, S. O.; Simanek, E. E. Structure-activity relationships in dendrimers based on triazines: Gelation depends on choice on linking and surface groups. *Macromolecules* **2002**, 35, 9015-9021.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	G4	Cl displacement of CC by amines	Branching	C	<i>J. Am. Chem. Soc.</i>	Aug. 15, 2002

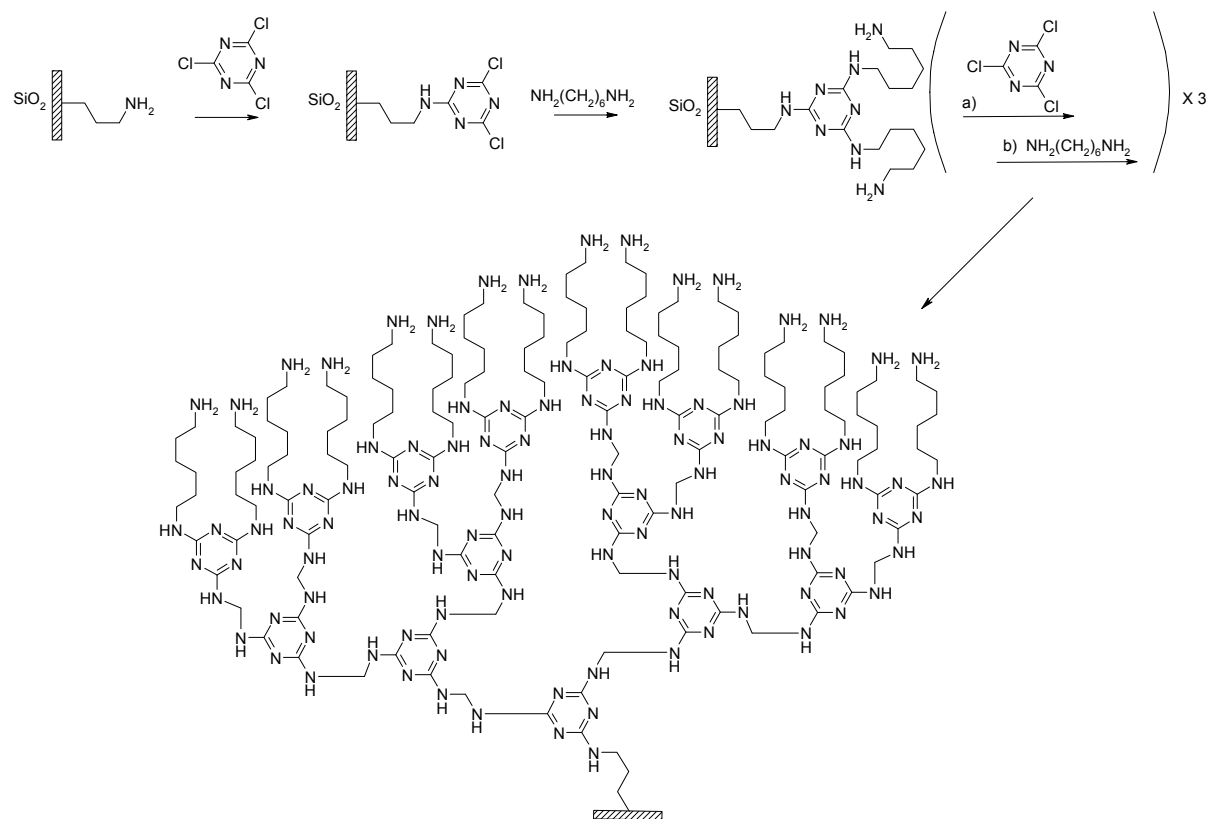
Zhang, W.; Tichey, S. E.; Pérez, L. M.; Maria, G. C.; Lindahl, P. A.; Simanek, E. E. Evaluation of multivalent dendrimers based on melamine: Kinetics of thiol-disulfide exchange depends on the structure of the dendrimer. *J. Am. Chem. Soc.* **2003**, *125*, 5086-5094.





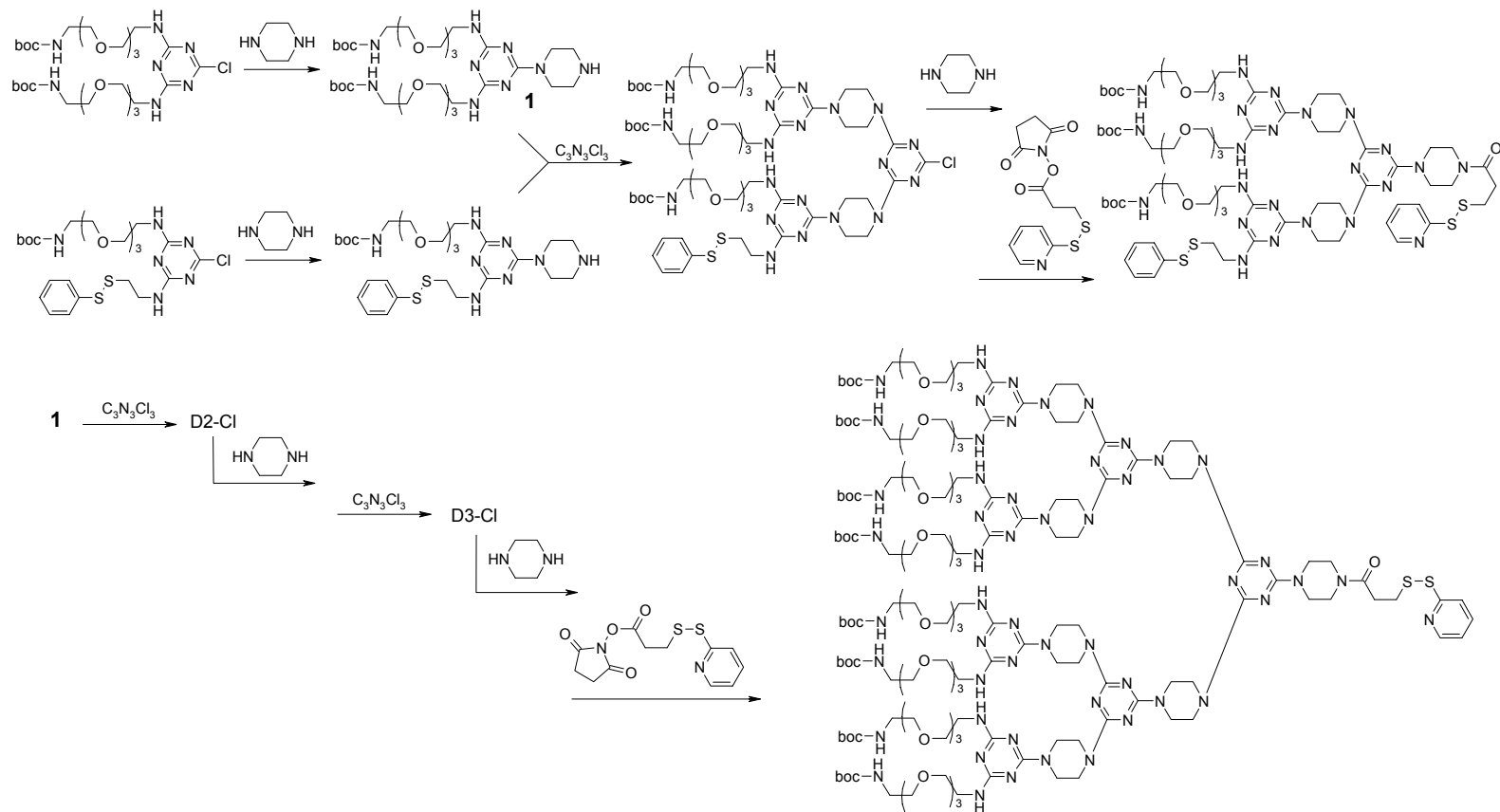
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Su	D4	Cl displacement of CC by amines	Branching	D	<i>Anal. Lett.</i>	Sept. 6, 2002

Wu, X.; Liu, P.; Pu, Q.; Su, Z. FAAS determination of platinum using an on-line separation and preconcentration system with a polymelamine dendrimer immobilized silica gel. *Anal. Lett.* **2003**, 36, 2229-2241.



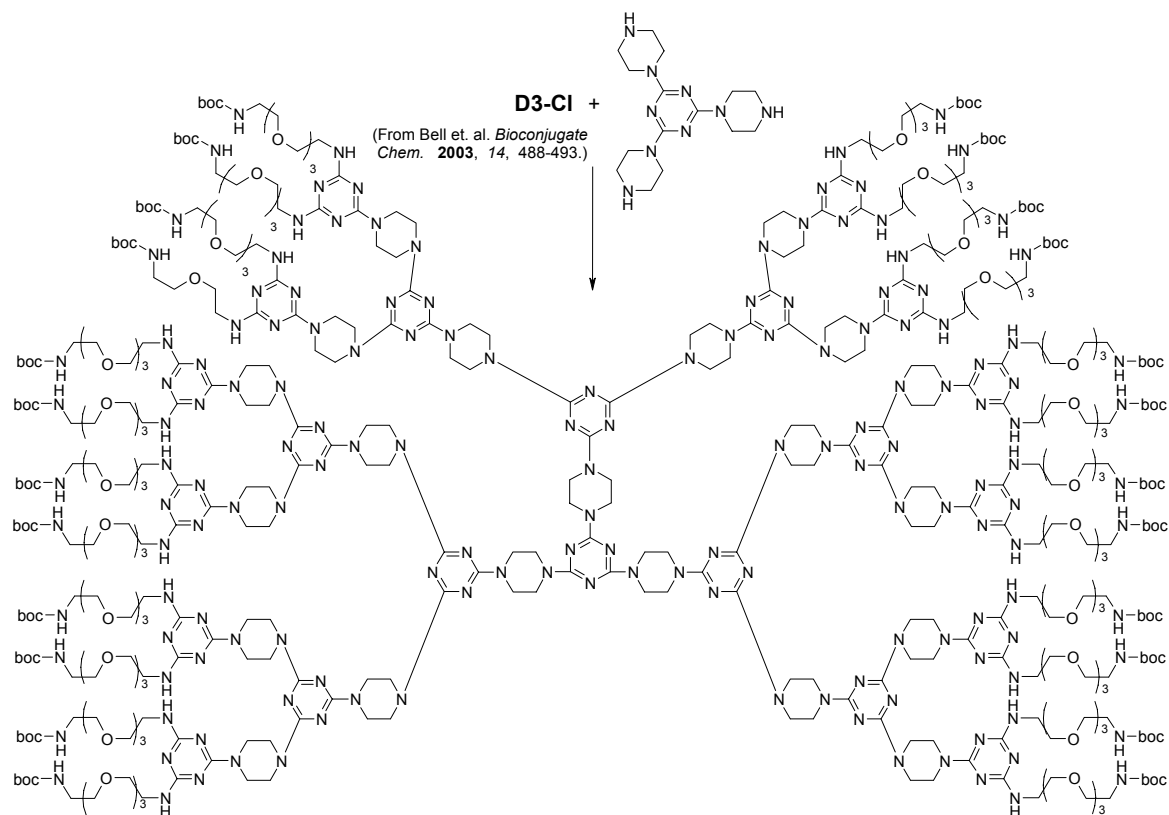
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	D3	Cl displacement of CC by amines	Branching	C	<i>Bioconjugate Chem.</i>	Sept. 25, 2002

Bell, S. A.; McLean, M. E.; Oh, S.-K.; Tichy, S. E.; Zhang, W.; Corn, R. M.; Crooks, R. M.; Simanek, E. E. Synthesis and characterization of covalently linked single-stranded DNA oligonucleotide-dendron conjugates. *Bioconjugate Chem.* **2003**, *14*, 488-493.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	G3	Cl displacement of CC by amines	Branching/ core	C	<i>Supramolecular Chemistry</i>	Nov. 2, 2002

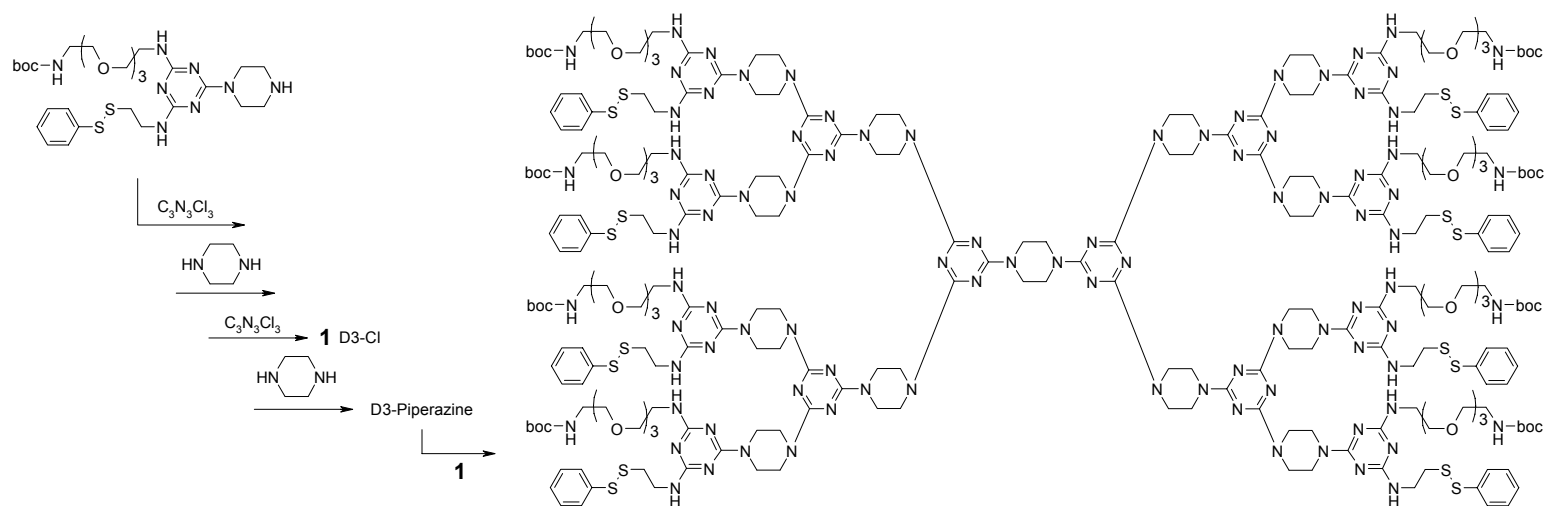
Zhang, W.; Jiang, J.; Qin, C.; Pérez, L. M.; Parrish, A. R.; Safe, S. H.; Simanek, E. E. Triazine dendrimers for drug delivery: Evaluation of solubilization properties, activity in cell culture, and *in vivo* toxicity of a candidate vehicle. *Supramolecular Chem.* **2003**, *15*, 607-616.





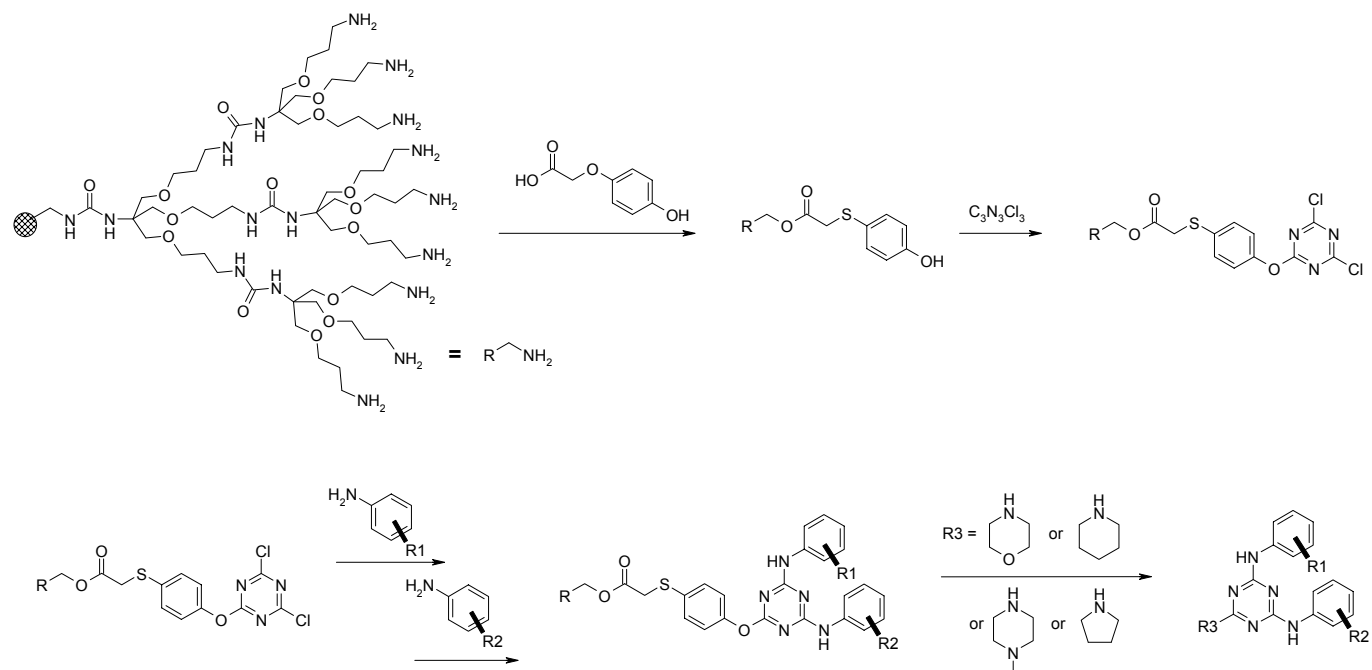
Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	G3	Cl displacement of CC by amines	Branching	C	<i>Org. Lett.</i>	Jan. 28, 2003

Umali, A. P.; Simanek, E. E. Thiol-disulfide exchange yields multivalent dendrimers of melamine. *Org. Lett.* **2003**, 5, 1245-1247.



Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Bradley	D3	Cl displacement of CC by aryl O	Surface	D	<i>Tetrahedron</i>	Feb. 7, 2003

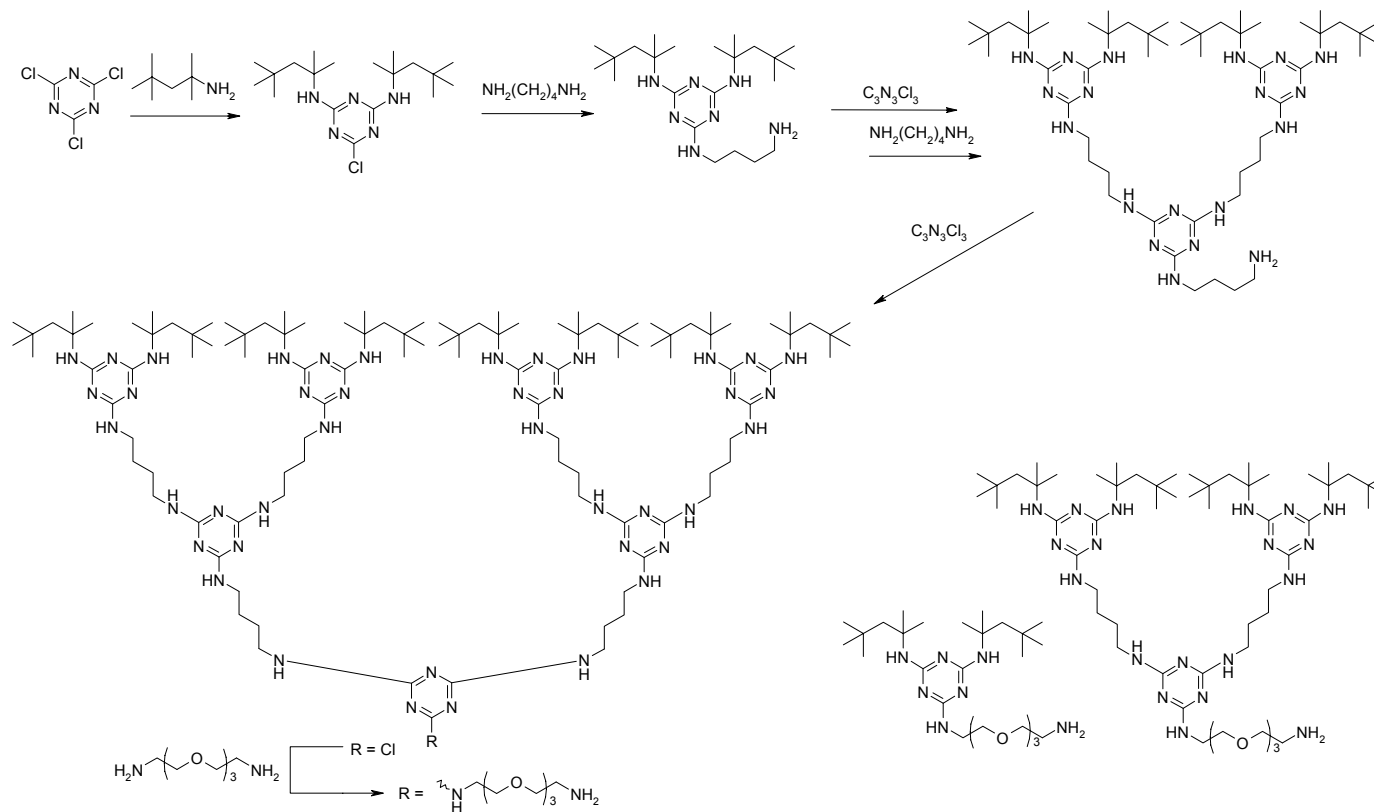
Lebreton, S.; Newcombe, N.; Bradley, M. Antibacterial single-bead screening. *Tetrahedron* **2003**, 59, 10213-10222.



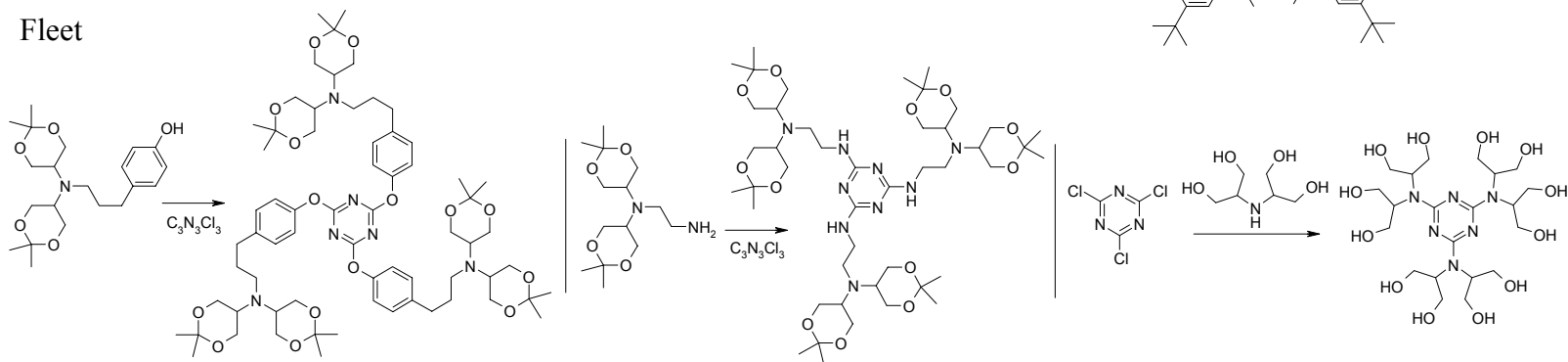
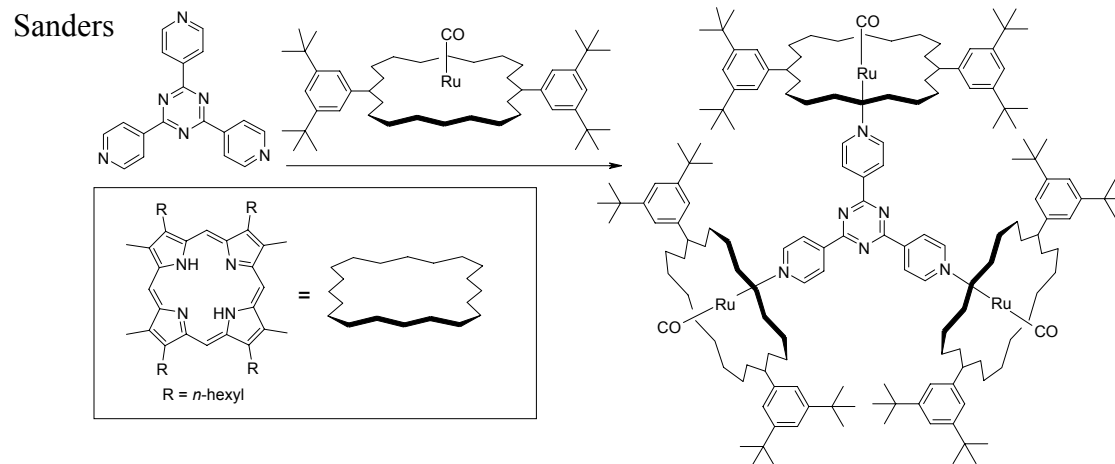
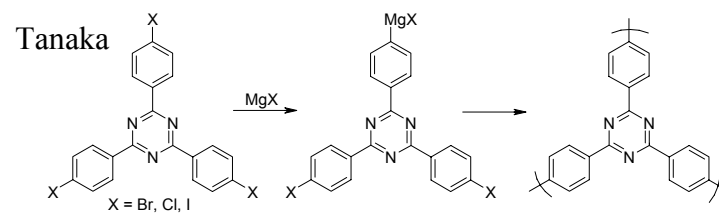
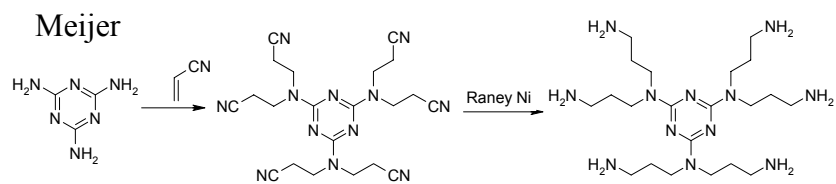


Group	Size	Method of Synthesis	Triazine location	C/D	Journal/Patent	Date submitted
Simanek	D3	Cl displacement of CC by amines	Branching	C	<i>Chem. Mater.</i>	Feb. 19, 2003

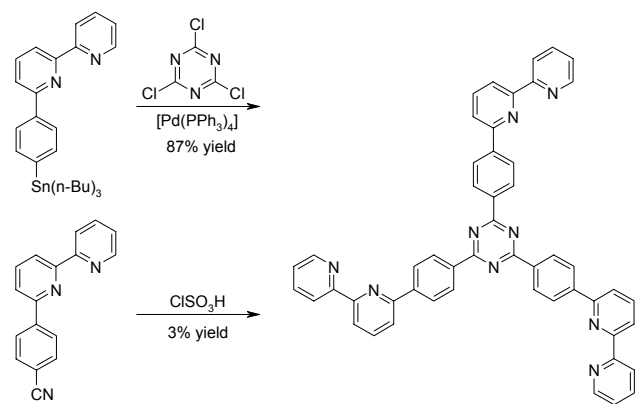
Acosta, E. J.; Deng, Y.; White, G. N.; Dixon, J. B.; McInnes, K. J.; Senseman, S. A.; Frantzen, A. S.; Simanek, E. E. Dendritic surfactants show evidence for frustrated intercalation: A new organoclay morphology. *Chem. Mater.* **2003**, *15*, 2903-2909.



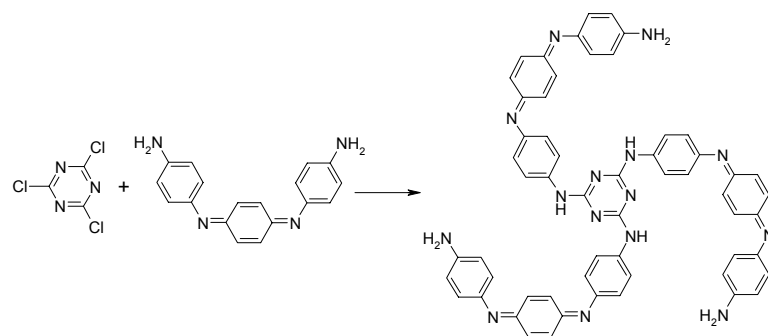
## OTHER 'SUGGESTED' TRIAZINE DENDRIMERS



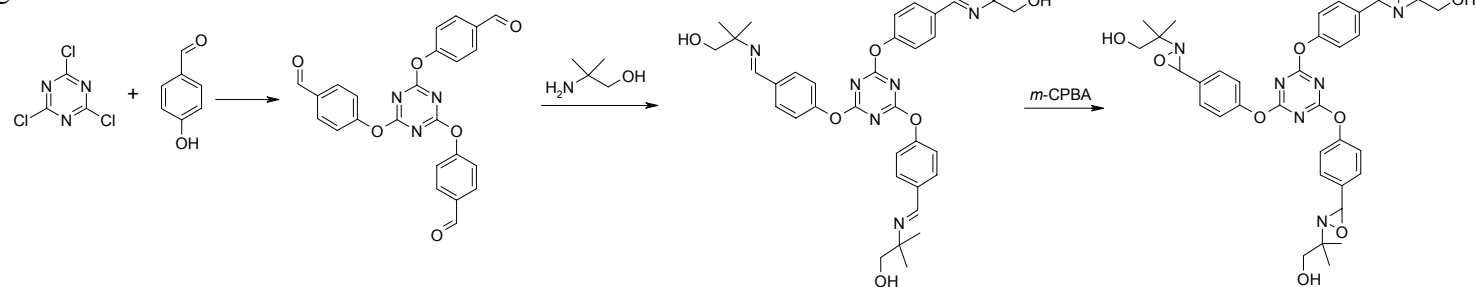
### Constable/Housecroft



### Viswanathan



### Balogh-Nair



Nobel Prizes awarded for work involving natural and synthetic polymers		
<b>2003</b> Peter Agre, Roderick MacKinnon	"for discoveries concerning channels in cell membranes" "for the discovery of water channels"	"for structural and mechanistic studies of ion channels"
<b>2002</b> John B. Fenn, Koichi Tanaka, Kurt Wüthrich	"for their development of soft desorption ionisation methods for mass spectrometric analyses of biological macromolecules"	"for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution"
<b>2000</b> Alan Heeger, Alan G. MacDiarmid, Hideki Shirakawa	"for the discovery and development of conductive polymers"	
<b>1997</b> Paul D. Boyer, John E. Walker, Jens C. Skou	"for their elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)"	"for the first discovery of an ion-transporting enzyme, Na <sup>+</sup> , K <sup>+</sup> -ATPase"
<b>1993</b> Kary B. Mullis, Michael Smith	"for contributions to the developments of methods within DNA-based chemistry""for his invention of the polymerase chain reaction (PCR) method"	"for his fundamental contributions to the establishment of oligonucleotide-based, site-directed mutagenesis and its development for protein studies"
<b>1991</b> Richard R. Ernst	"for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy"	
<b>1990</b> Elias James Corey	"for his development of the theory and methodology of organic synthesis"	
<b>1989</b> Sidney Altman, Thomas R. Cech	"for their discovery of catalytic properties of RNA"	
<b>1988</b> Johann Deisenhofer, Robert Huber, Hartmut Michel	"for the determination of the three-dimensional structure of a photosynthetic reaction centre"	
<b>1987</b> Donald J. Cram, Jean-Marie Lehn, Charles J. Pedersen	"for their development and use of molecules with structure-specific interactions of high selectivity"	
<b>1985</b> Herbert A. Hauptman, Jerome Karle	"for their outstanding achievements in the development of direct methods for the determination of crystal structures"	
<b>1984</b> Bruce Merrifield	"for his development of methodology for chemical synthesis on a solid matrix"	
<b>1982</b> Aaron Klug	"for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes"	
<b>1980</b> Paul Berg, Walter Gilbert, Frederick Sanger	"for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA"	"for their contributions concerning the determination of base sequences in nucleic acids"
<b>1974</b> Paul J. Flory	"for his fundamental achievements, both theoretical and experimental, in the physical chemistry of the macromolecules"	
<b>1972</b> Christian Anfinsen, Stanford Moore, William H. Stein	"for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation"	"for their contribution to the understanding of the connection between chemical structure and catalytic activity of the active centre of the ribonuclease molecule"
<b>1970</b> Luis Leloir	"for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates"	
<b>1965</b> Robert B. Woodward	"for his outstanding achievements in the art of organic synthesis"	
<b>1964</b> Dorothy Crowfoot Hodgkin	"for her determinations by X-ray techniques of the structures of important biochemical substances"	
<b>1963</b> Karl Ziegler, Giulio Natta	"for their discoveries in the field of the chemistry and technology of high polymers"	
<b>1962</b> Francis Crick, James Watson, Maurice Wilkins	"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"	
<b>1962</b> Max F. Perutz, John C. Kendrew	"for their studies of the structures of globular proteins"	

<b>1959</b> Severo Ochoa, Arthur Kornberg	"for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid"	
<b>1958</b> Frederick Sanger	"for his work on the structure of proteins, especially that of insulin"	
<b>1957</b> Lord Todd	"for his work on nucleotides and nucleotide co-enzymes"	
<b>1955</b> Vincent du Vigneaud	"for his work on biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone"	
<b>1954</b> Linus Pauling	"for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances"	
<b>1953</b> Hermann Staudinger	"for his discoveries in the field of macromolecular chemistry"	
<b>1948</b> Arne Tiselius	"for his research on electrophoresis and adsorption analysis, especially for his discoveries concerning the complex nature of the serum proteins"	
<b>1946</b> James B. Sumner, John H. Northrop, Wendell M. Stanley	"for his discovery that enzymes can be crystallized"	"for their preparation of enzymes and virus proteins in a pure form"
<b>1926</b> The Svedberg	"for his work on disperse systems"	
<b>1913</b> Alfred Werner	"in recognition of his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research especially in inorganic chemistry"	
<b>1902</b> Emil Fischer	"in recognition of the extraordinary services he has rendered by his work on sugar and purine syntheses"	

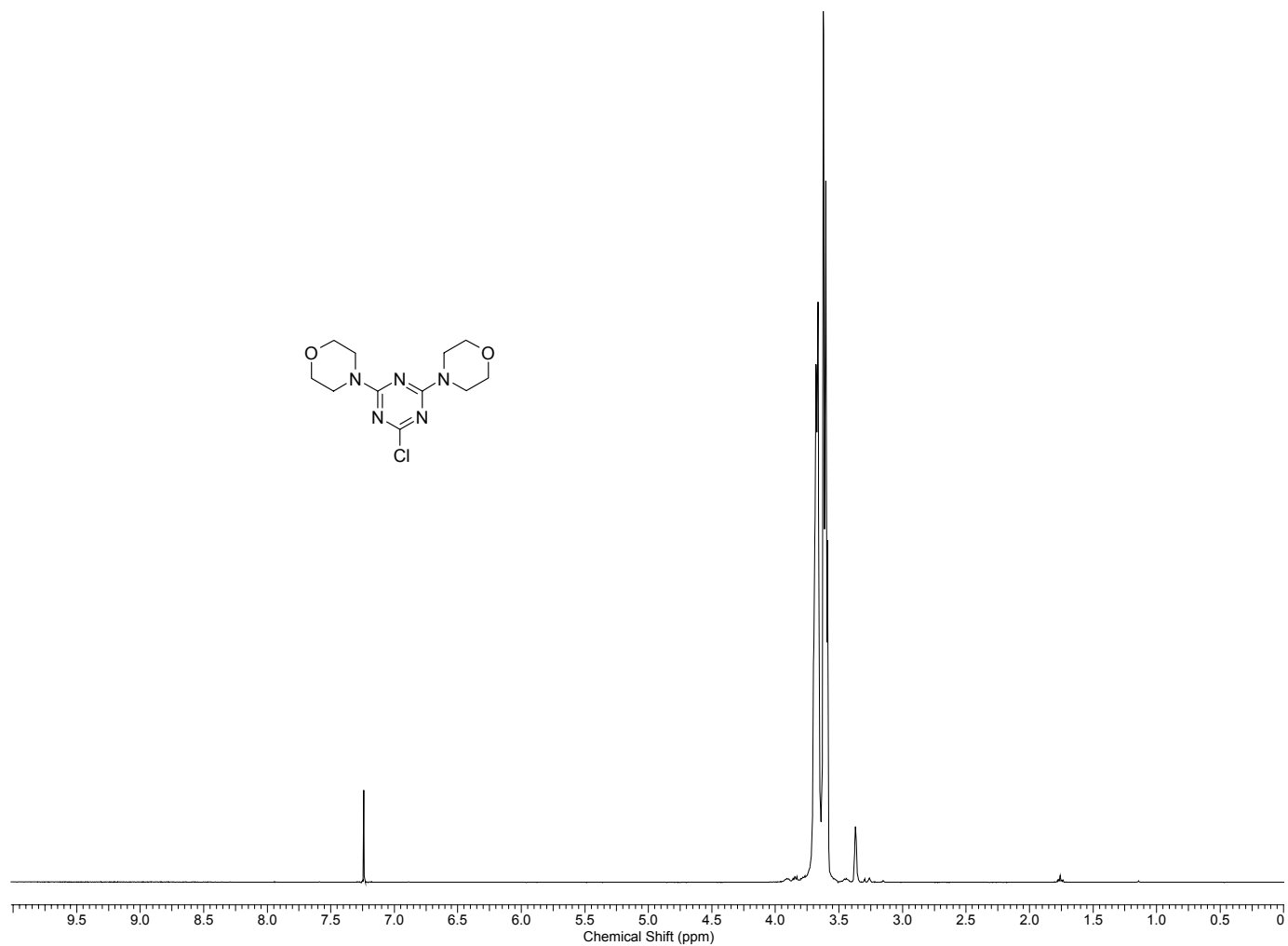
Dates in: **red** indicate awards given with a specific emphasis on polymers

**blue** are notable awards given for synthetic chemistry

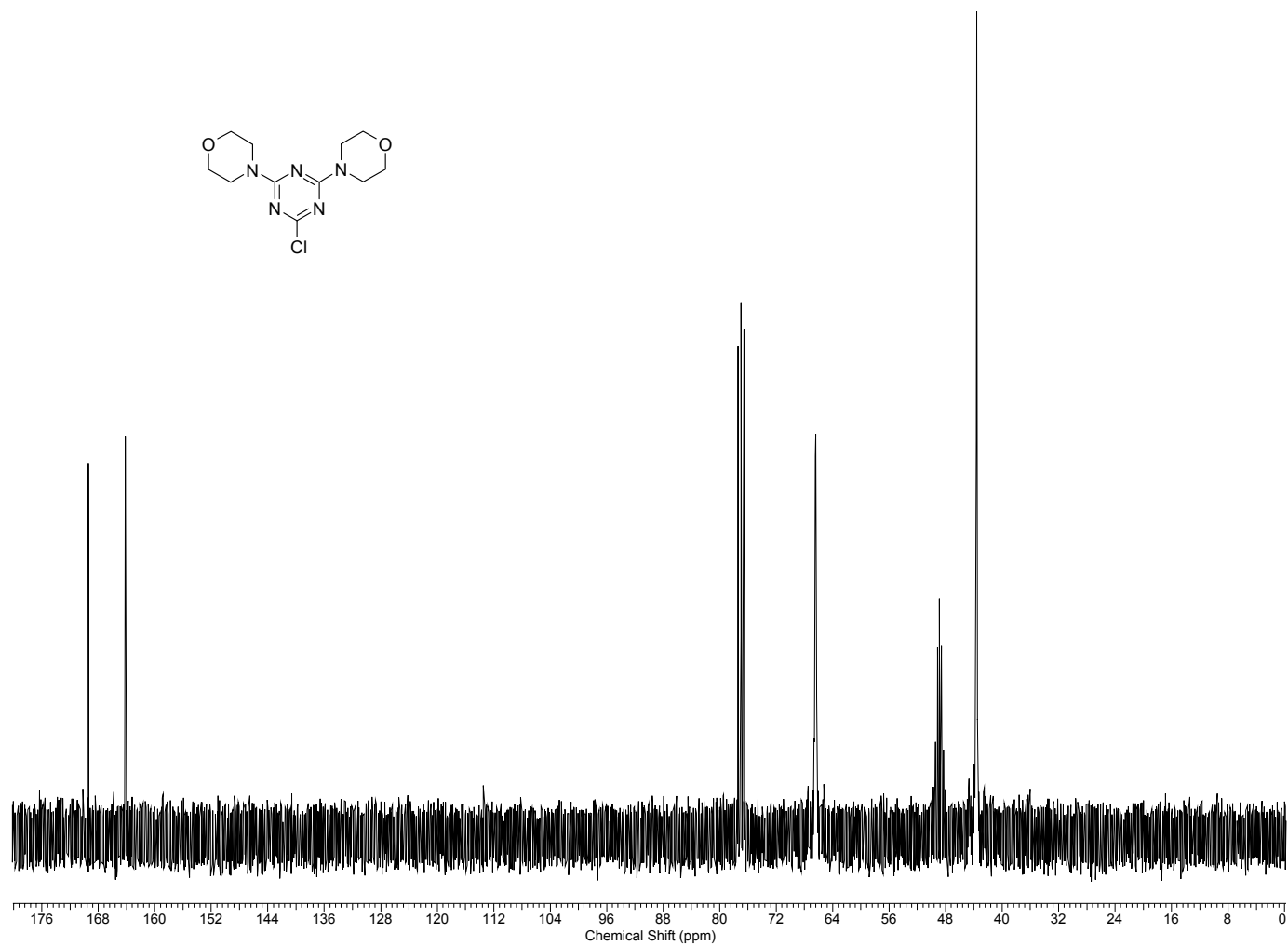
**orange** are awards given for analytical techniques for the study of polymers



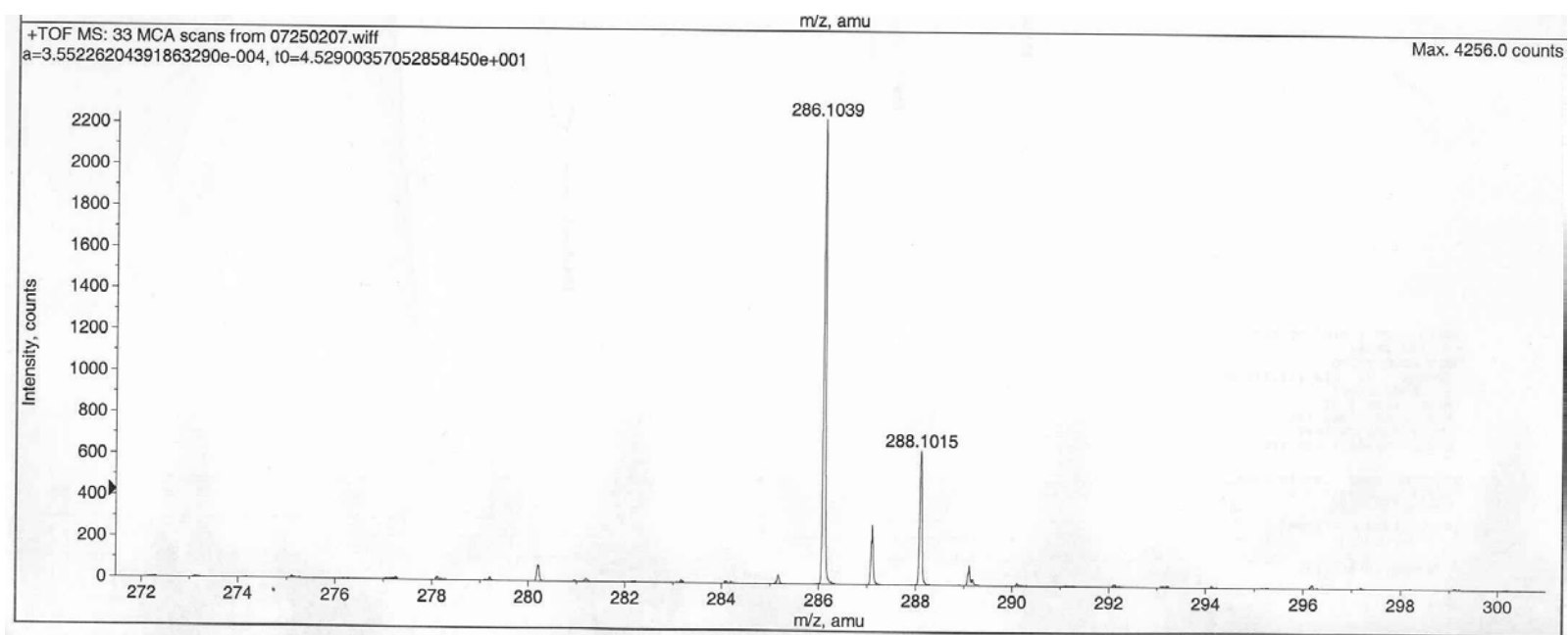
**APPENDIX B**  
**SPECTRA RELEVANT TO CHAPTER II**



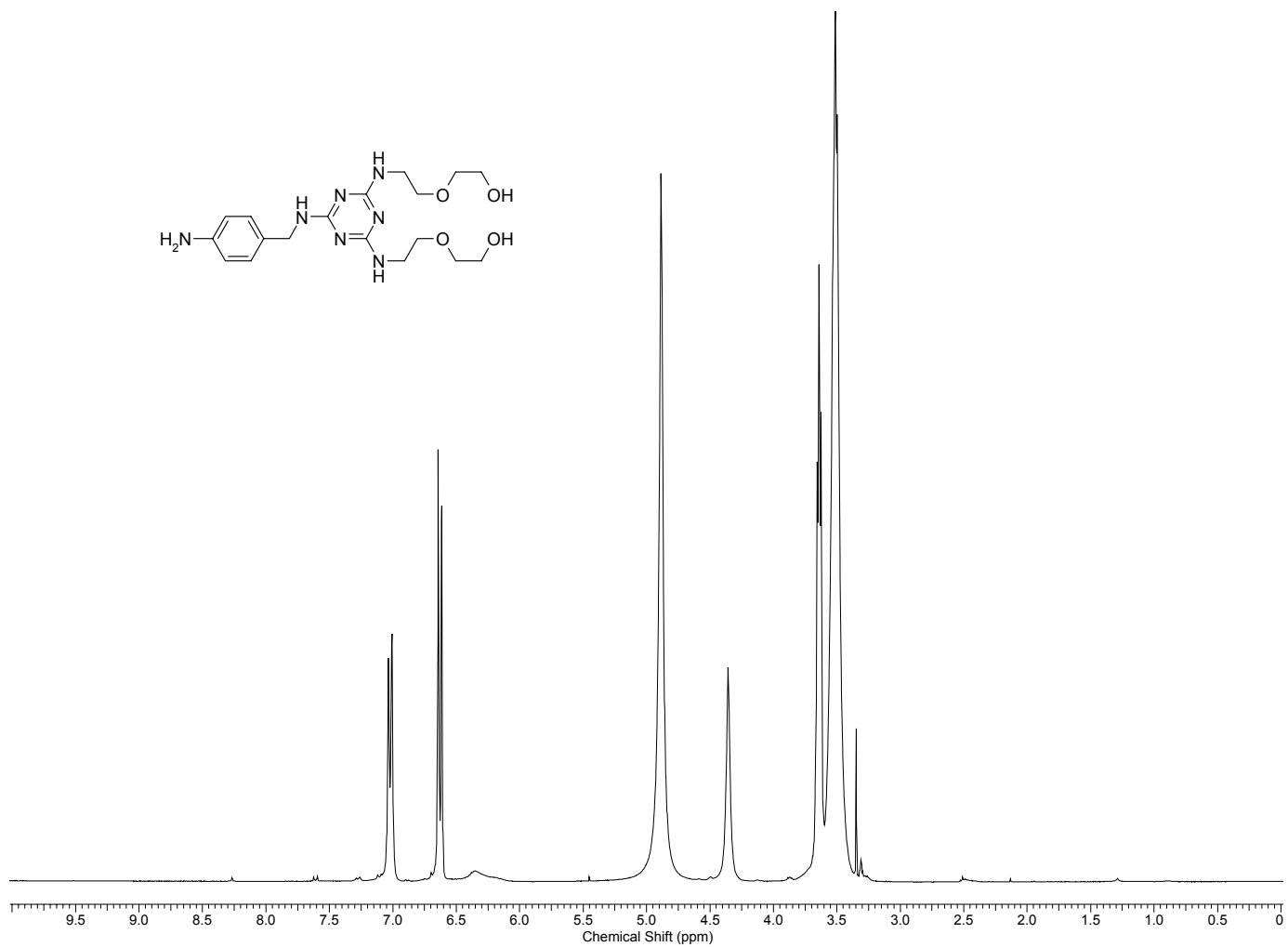
**Figure B.1a.** The  $^1\text{H}$  NMR spectrum of 2-Chloro-4,6-dimorpholino-1,3,5-triazine, **1** (300 MHz,  $\text{CDCl}_3$ ).



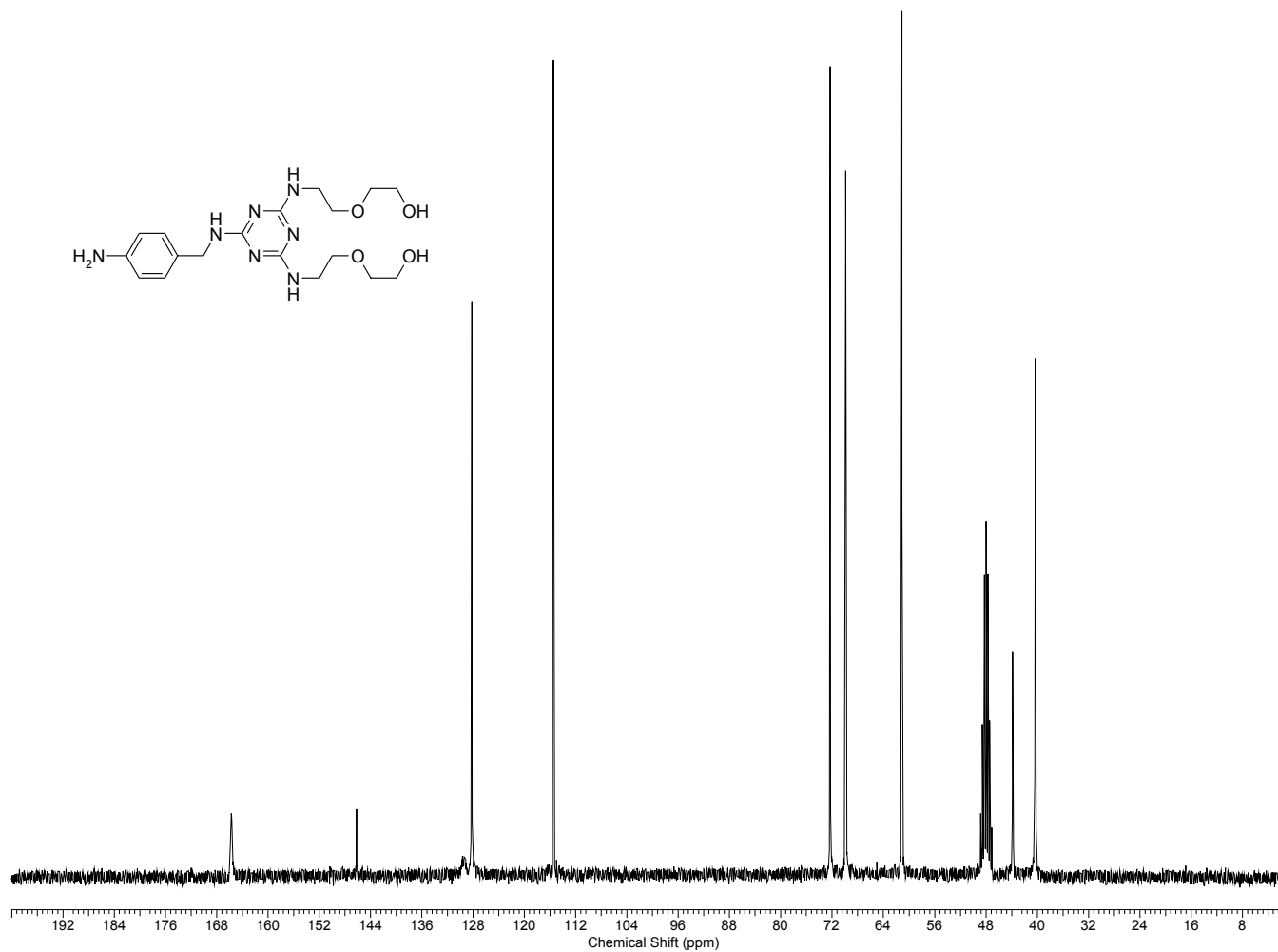
**Figure B.1b.** The <sup>13</sup>C NMR spectrum of 2-Chloro-4,6-dimorpholino-1,3,5-triazine, **1** (75 MHz, CDCl<sub>3</sub>).



**Figure B.1c.** The ESI-TOF mass spectrum of 2-Chloro-4,6-dimorpholino-1,3,5-triazine, **1**.



**Figure B.2a.** The  $^1\text{H}$  NMR spectrum of intermediate **15**. (300 MHz,  $\text{CD}_3\text{OD}$ )

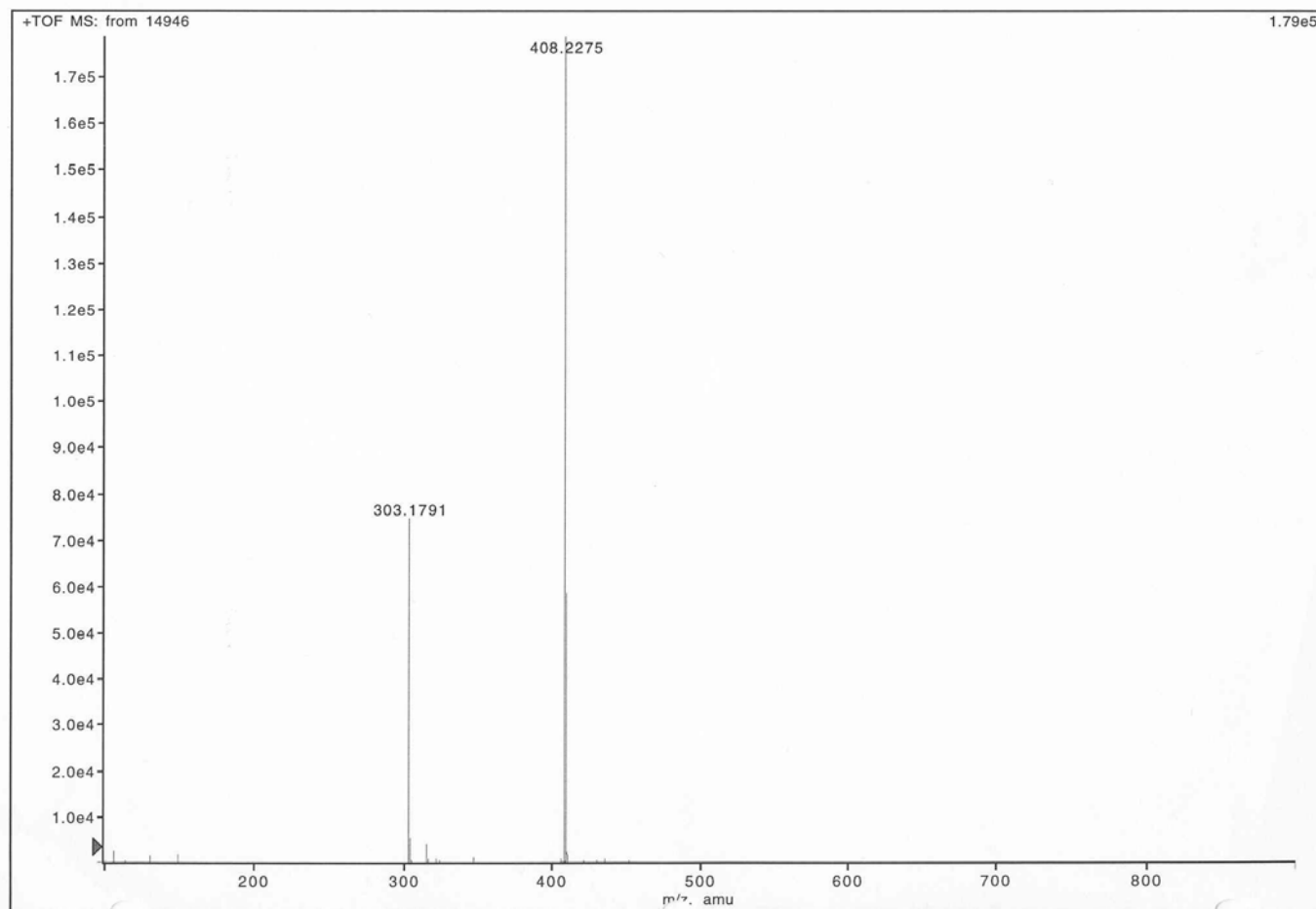


**Figure B.2b.** The  $^{13}\text{C}$  NMR spectrum of of intermediate **15**. (75 MHz,  $\text{CD}_3\text{OD}$ )

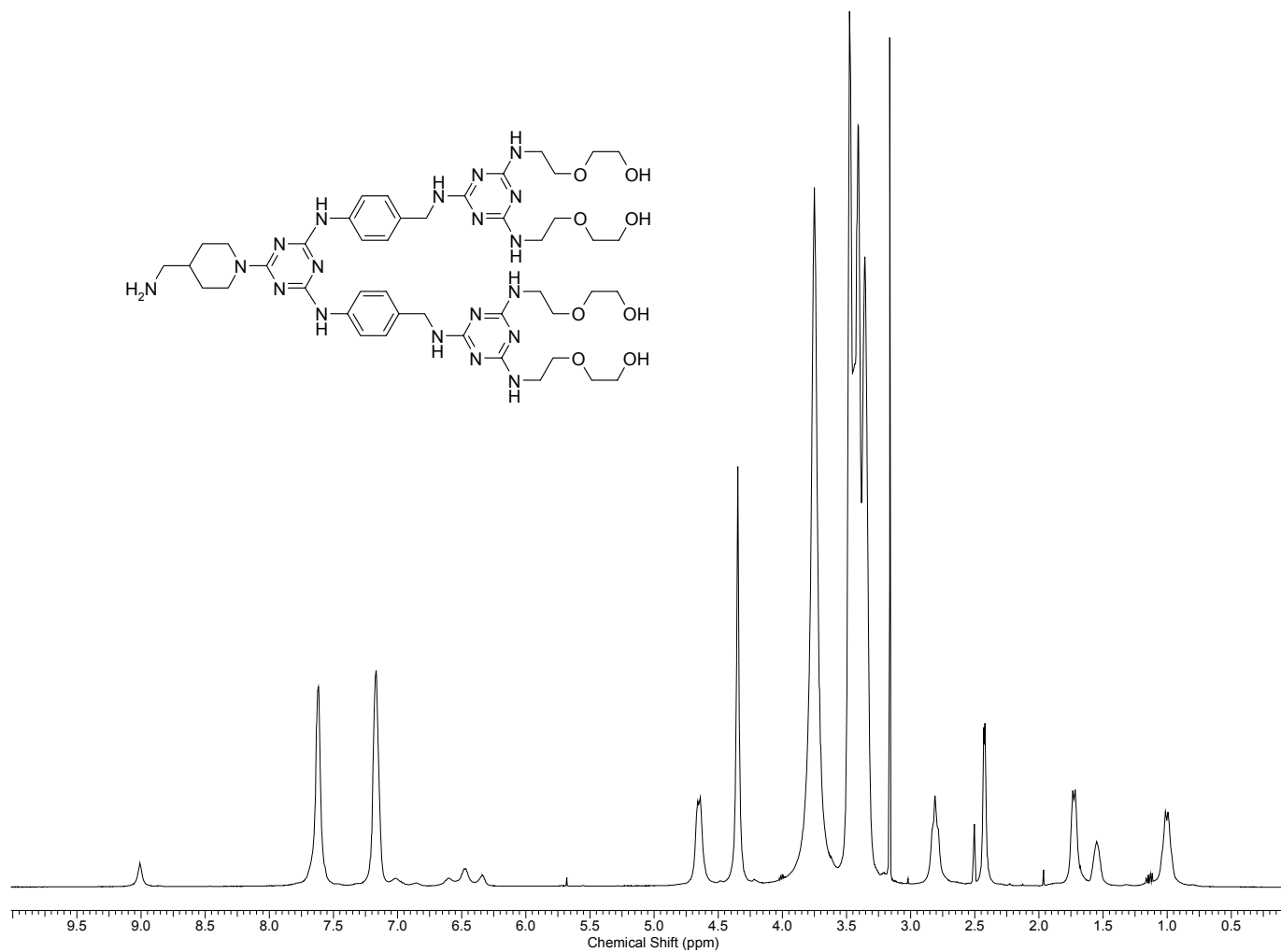
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Friday, January 26, 2001 10:09 AM

page 1 of 1

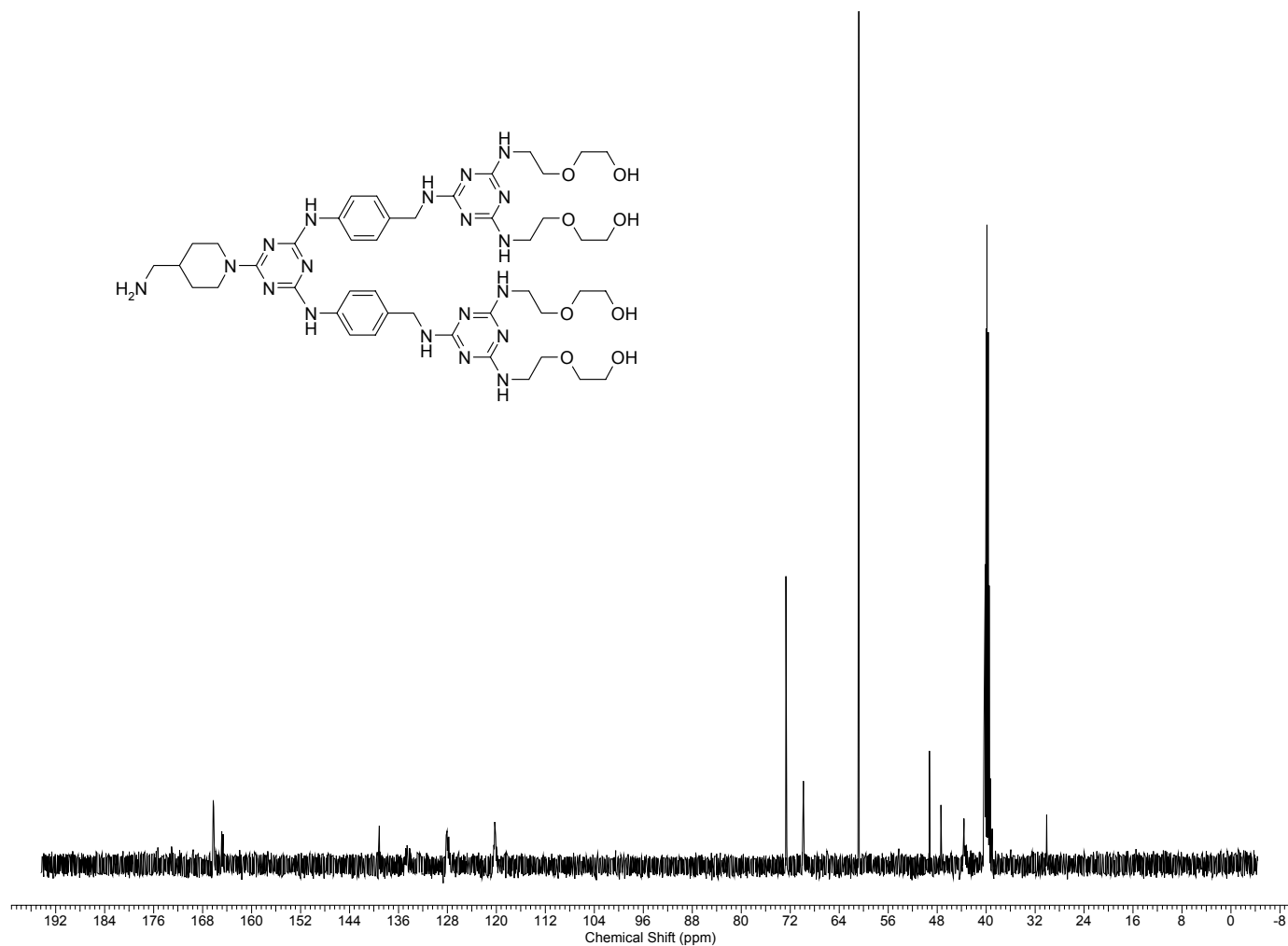


**Figure B.2c.** The ESI-TOF mass spectrum of intermediate **15**.

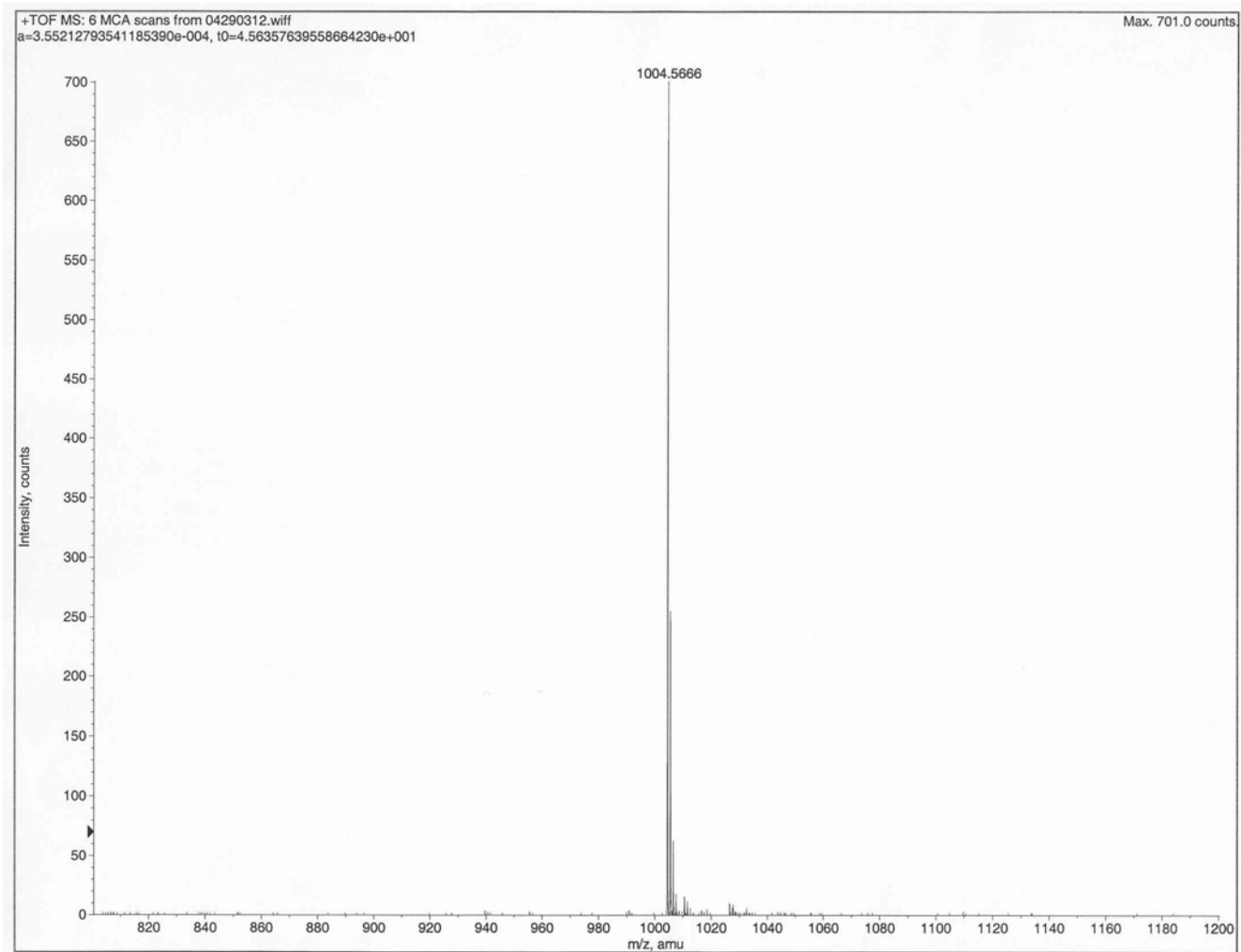


**Figure B.3a.** The  $^1\text{H}$  NMR spectrum of intermediate **16**. (300 MHz,  $\text{DMSO}-d_6$ )

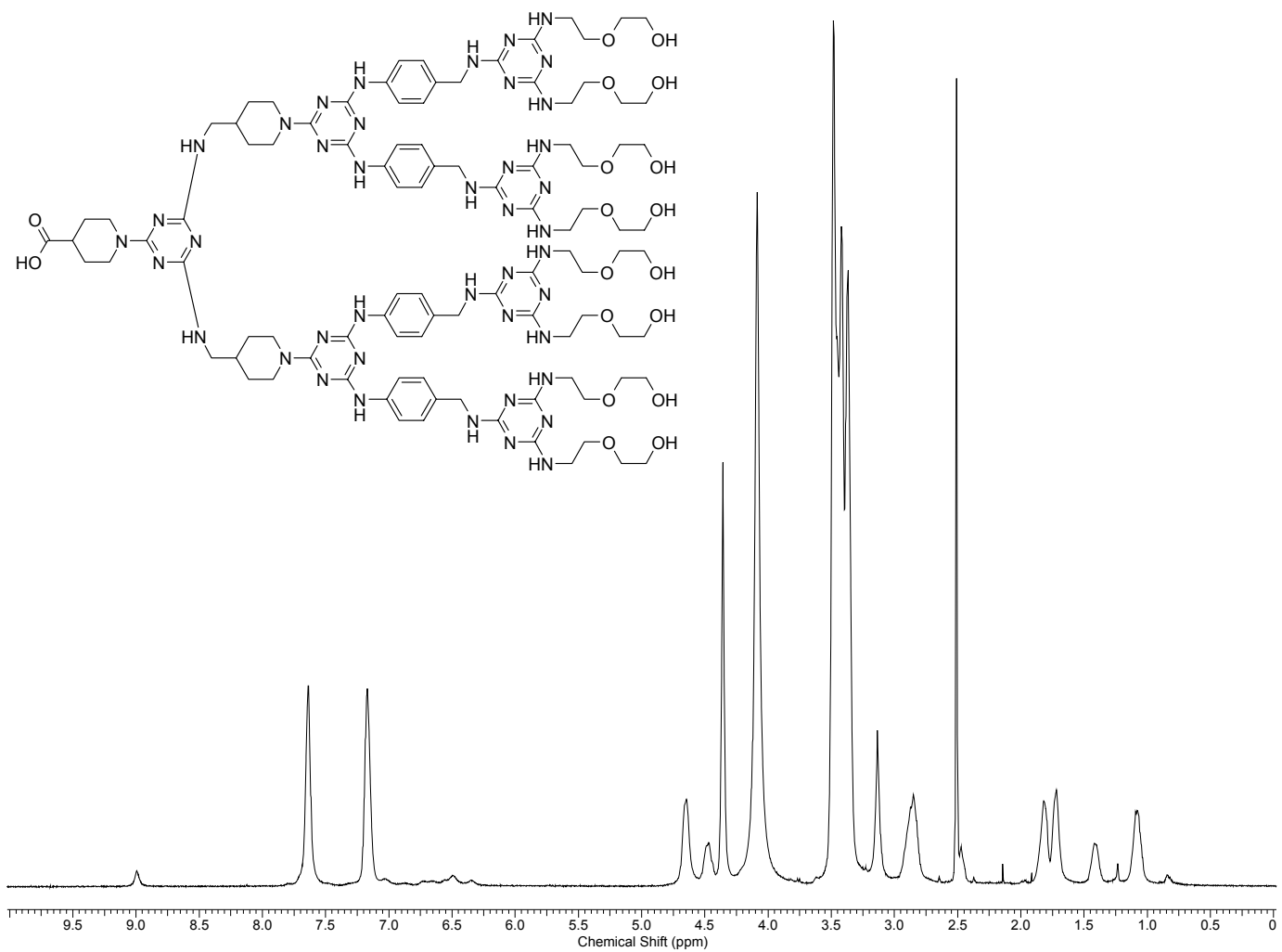




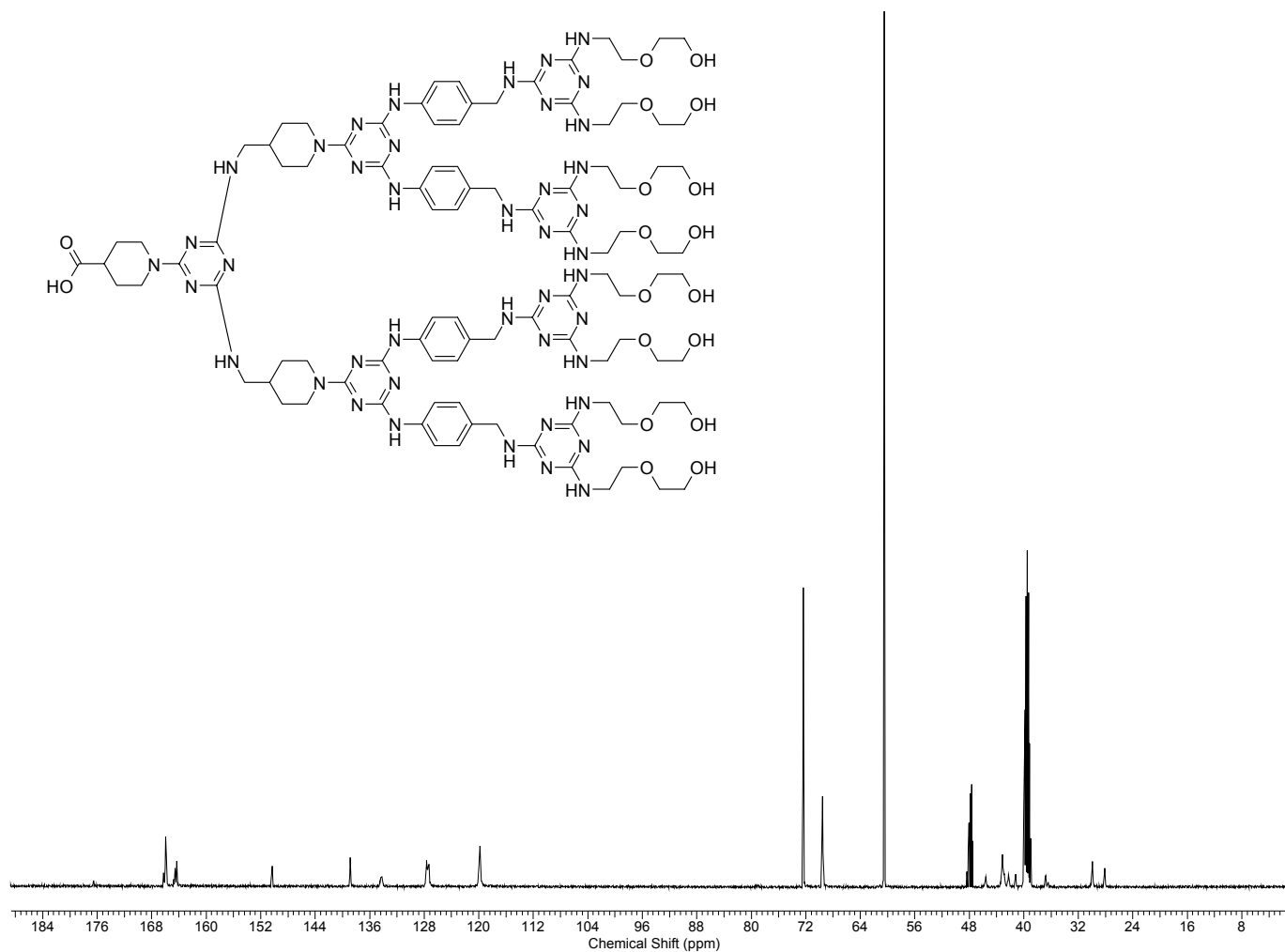
**Figure B.3b.** The  $^{13}\text{C}$  NMR spectrum of intermediate **16**. (125 MHz,  $\text{DMSO}-d_6$ )



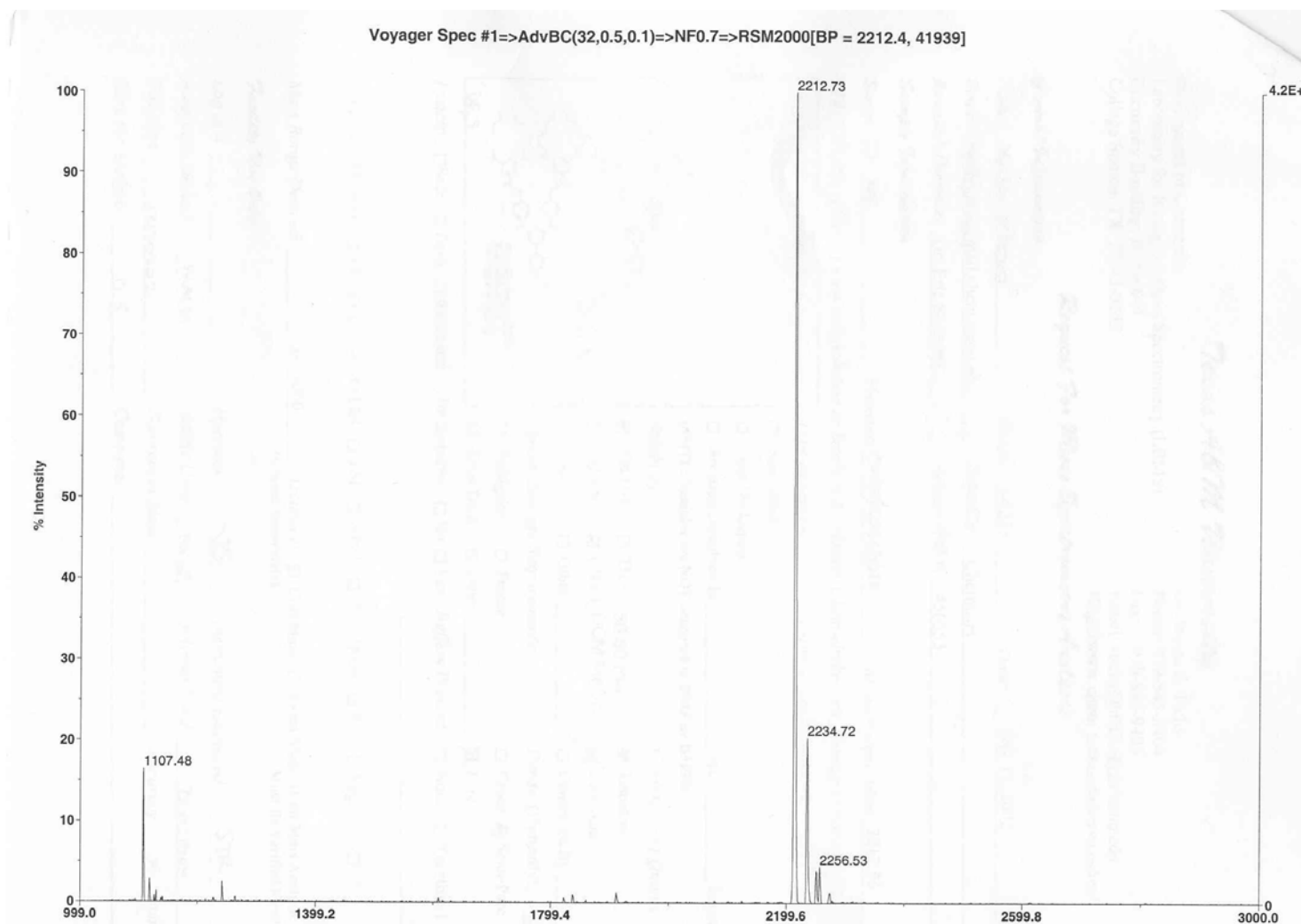
**Figure B.3c.** The ESI-TOF mass spectrum of intermediate **16**.



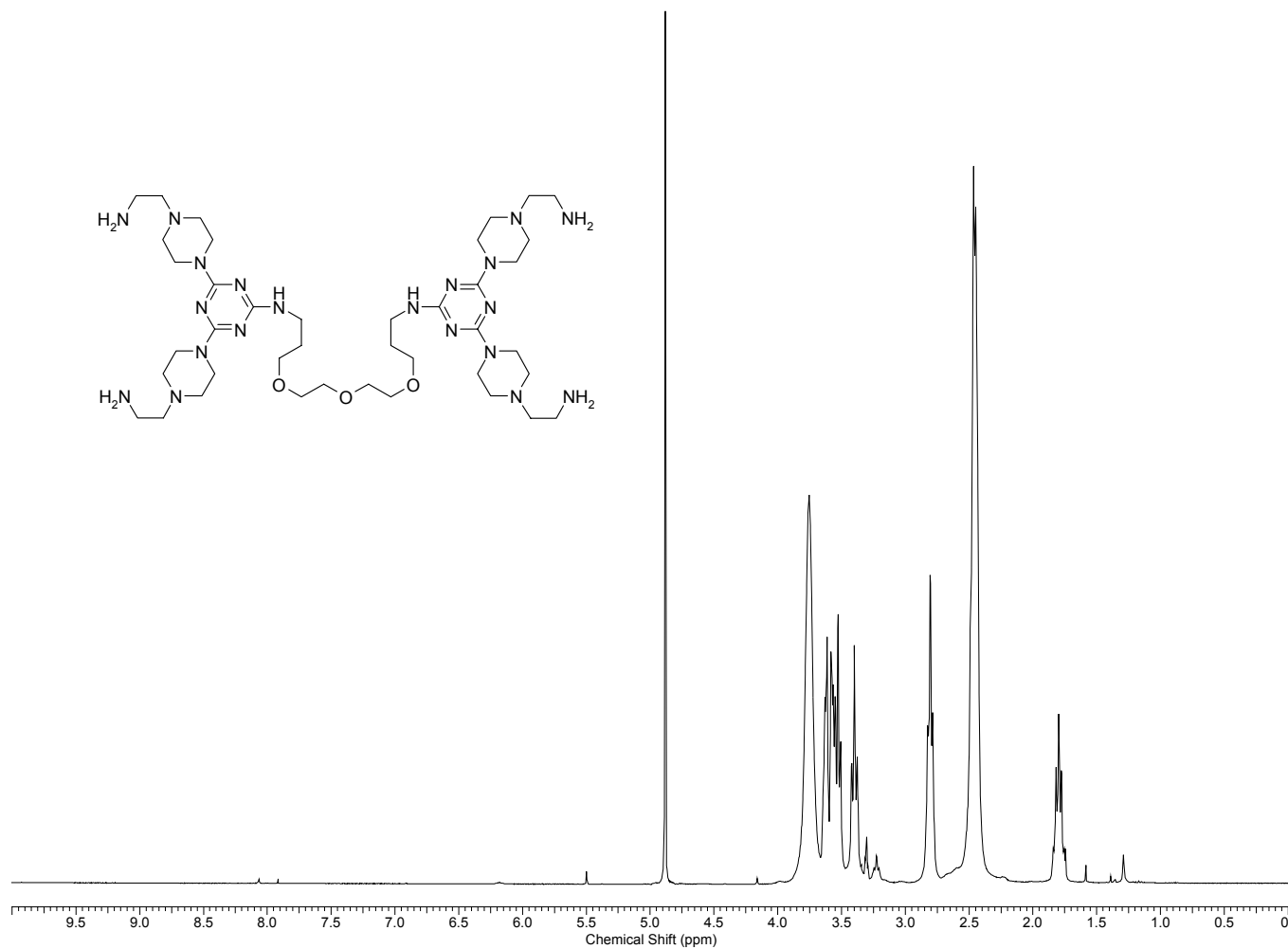
**Figure B.4a.** The  $^1\text{H}$  NMR spectrum of dendron **17**. (500 MHz,  $\text{DMSO-}d_6$ )



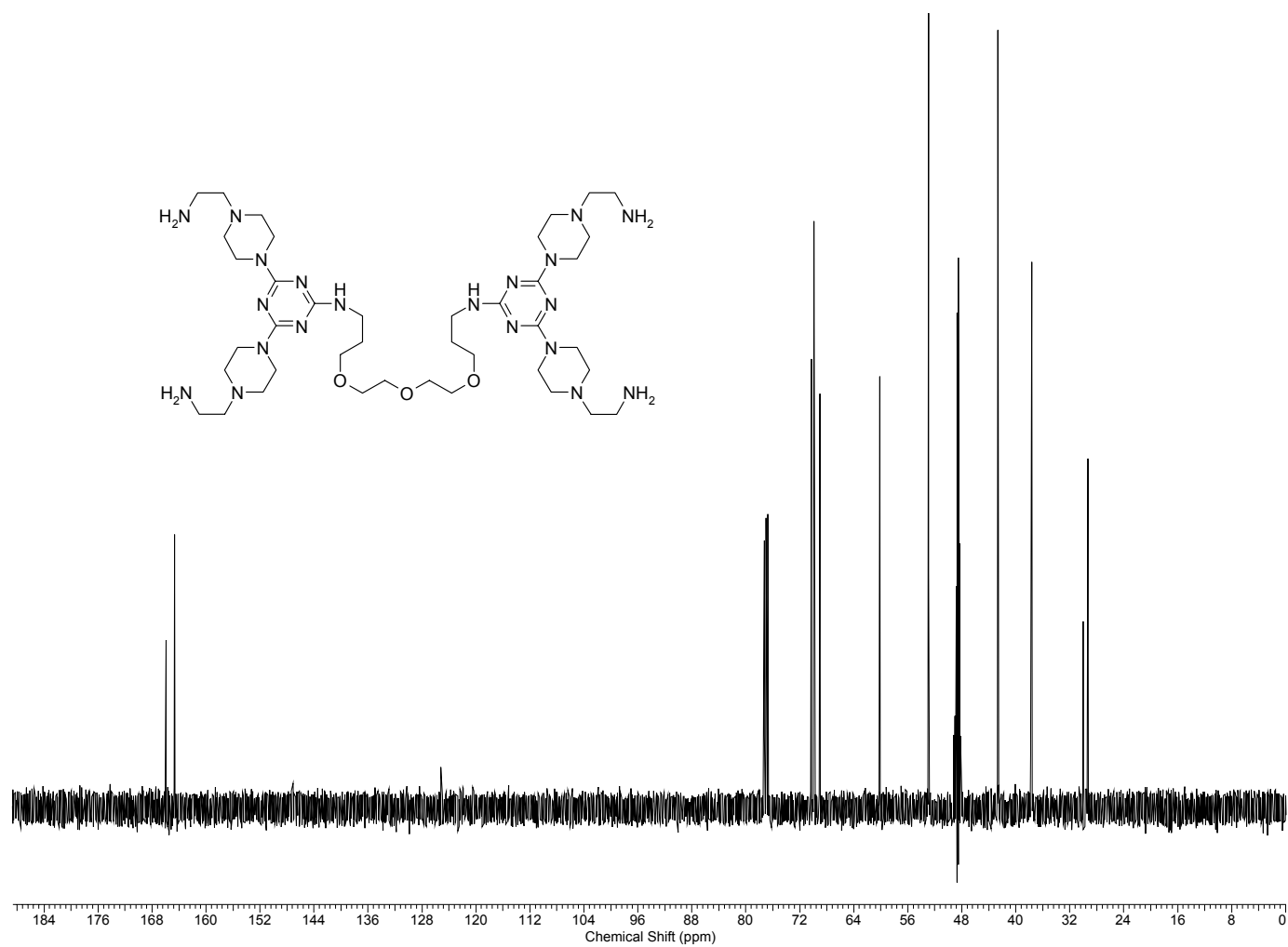
**Figure B.4b.** The  $^{13}\text{C}$  NMR spectrum of dendron 17. (125 MHz, DMSO- $d_6$ )



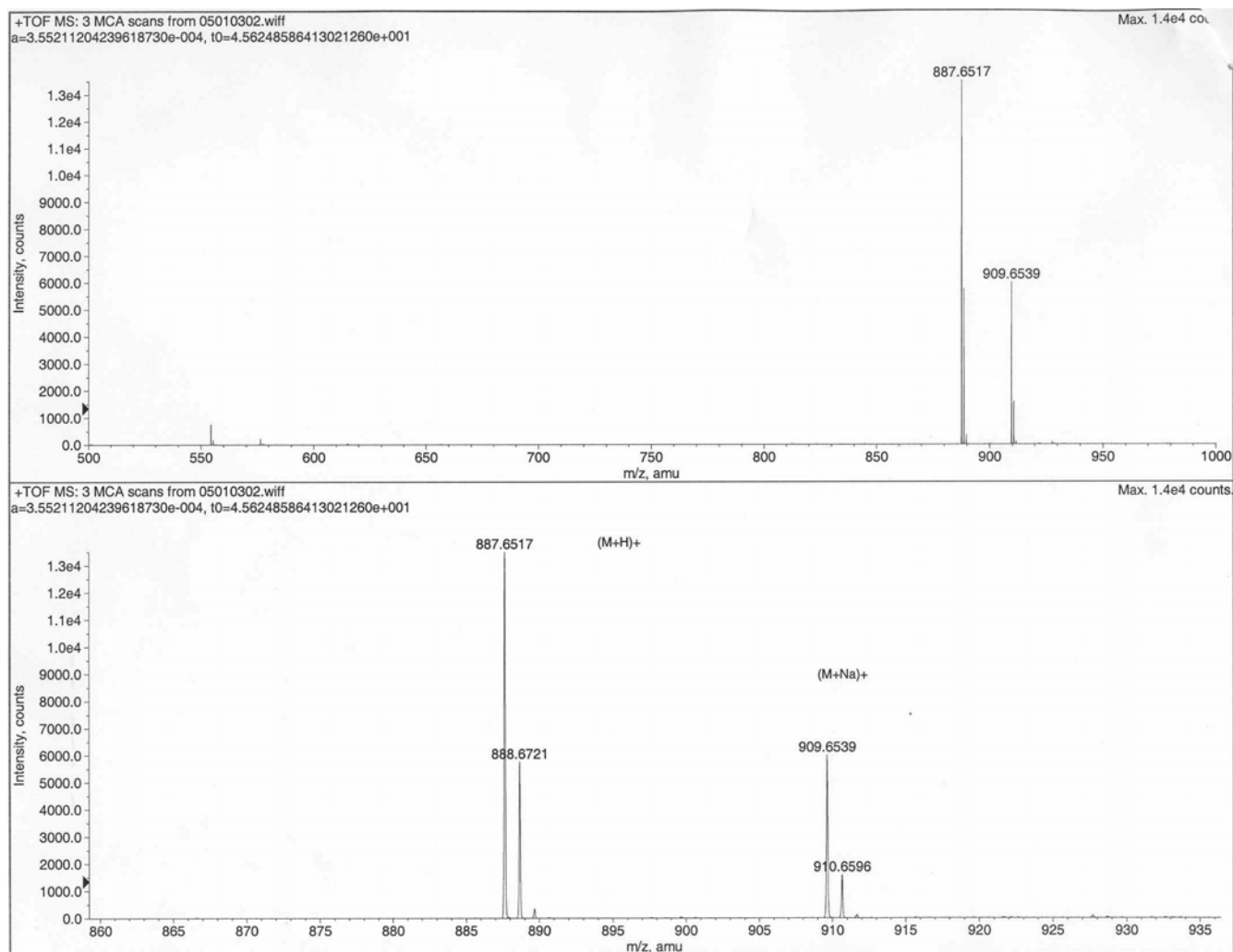
**Figure B.4c.** The MALDI-TOF mass spectrum of dendron **16**.



**Figure B.5a.** The  $^1\text{H}$  NMR spectrum of tetraamine core **18**. (300 MHz,  $\text{CD}_3\text{OD}$ )

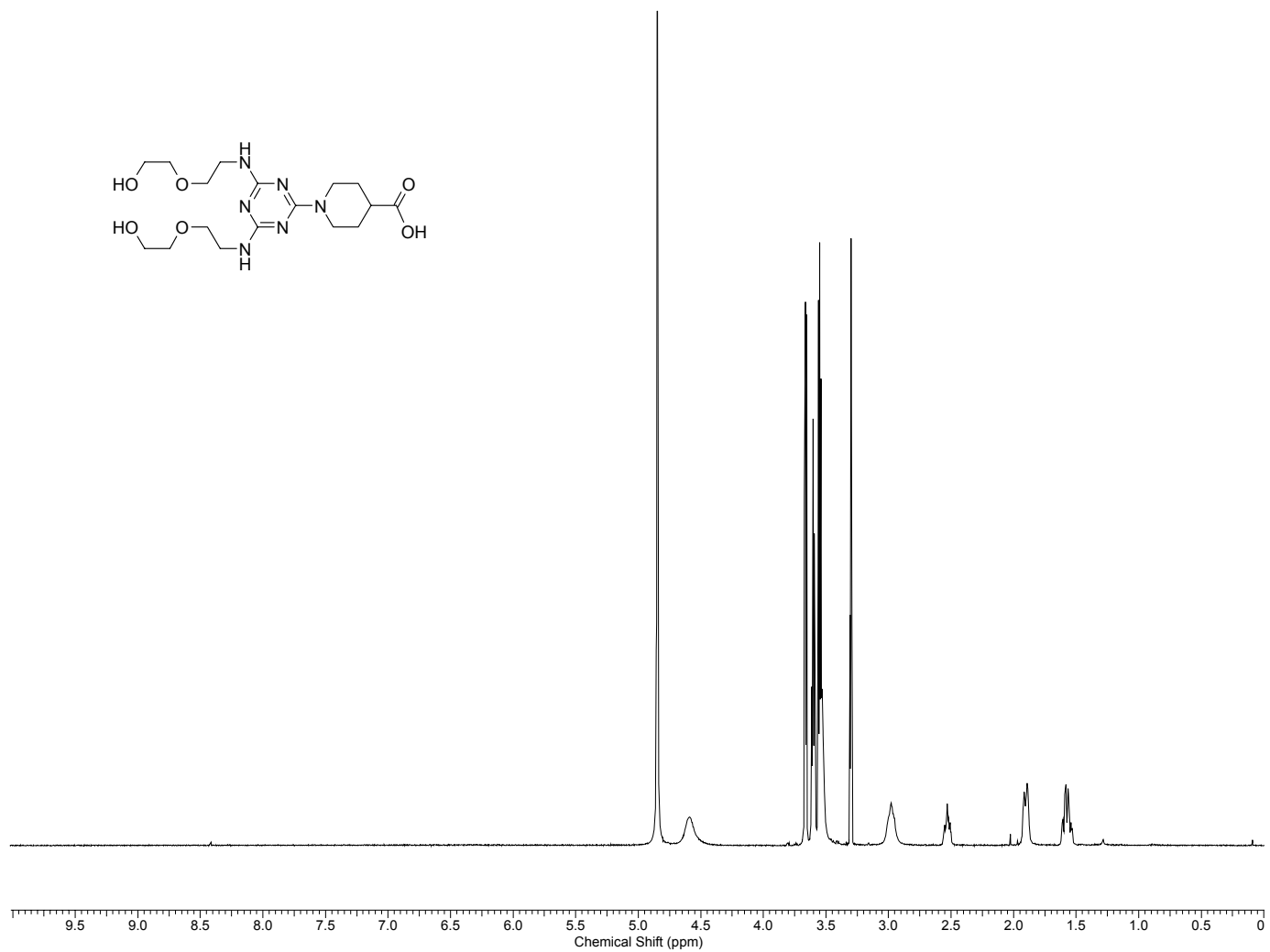


**Figure B.5b.** The  $^{13}\text{C}$  NMR spectrum of tetraamine core **18**. (300 MHz,  $\text{CD}_3\text{OD}$ )

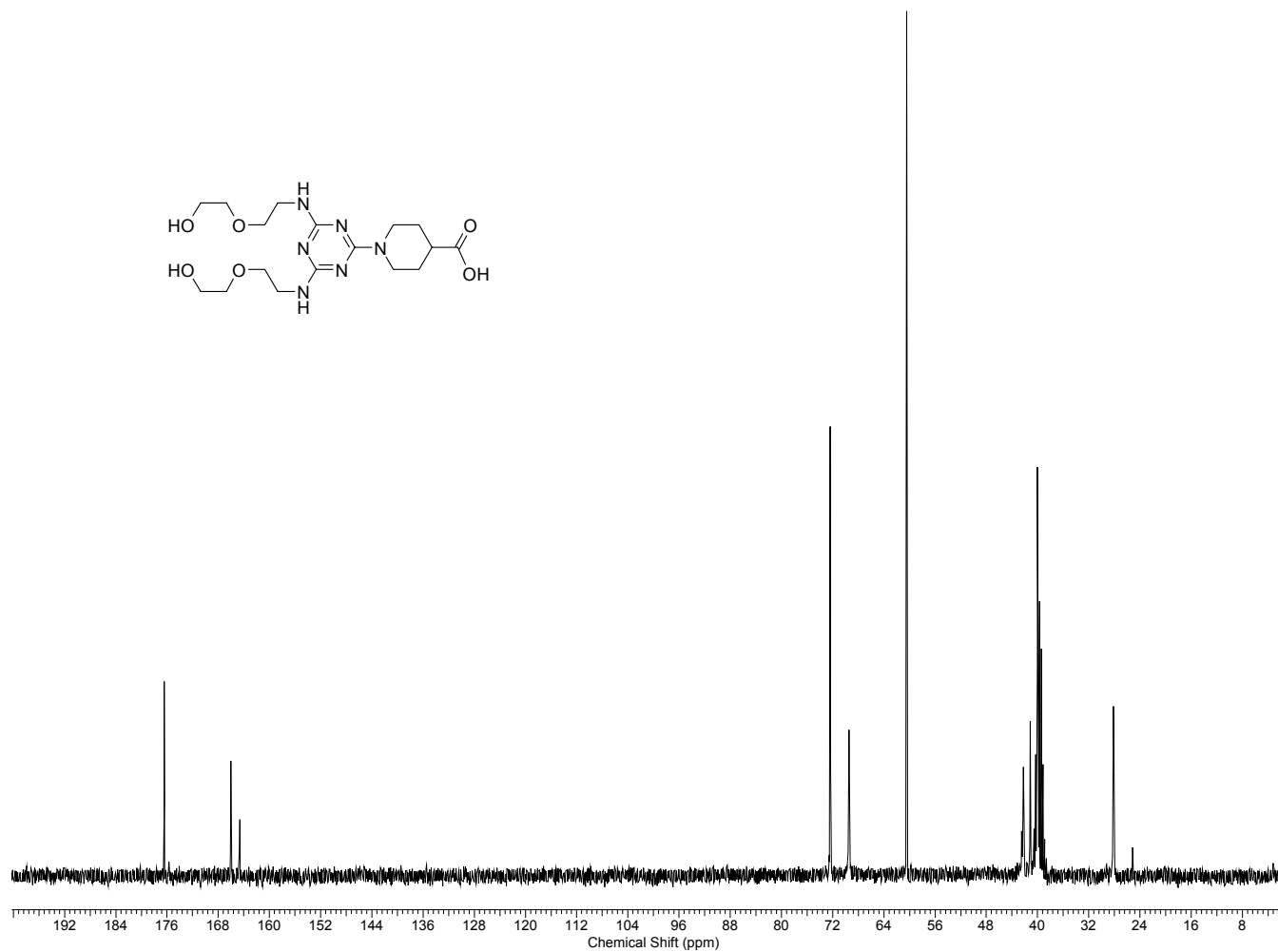


**Figure B.5c.** The ESI-TOF mass spectrum of tetraamine core **18**.

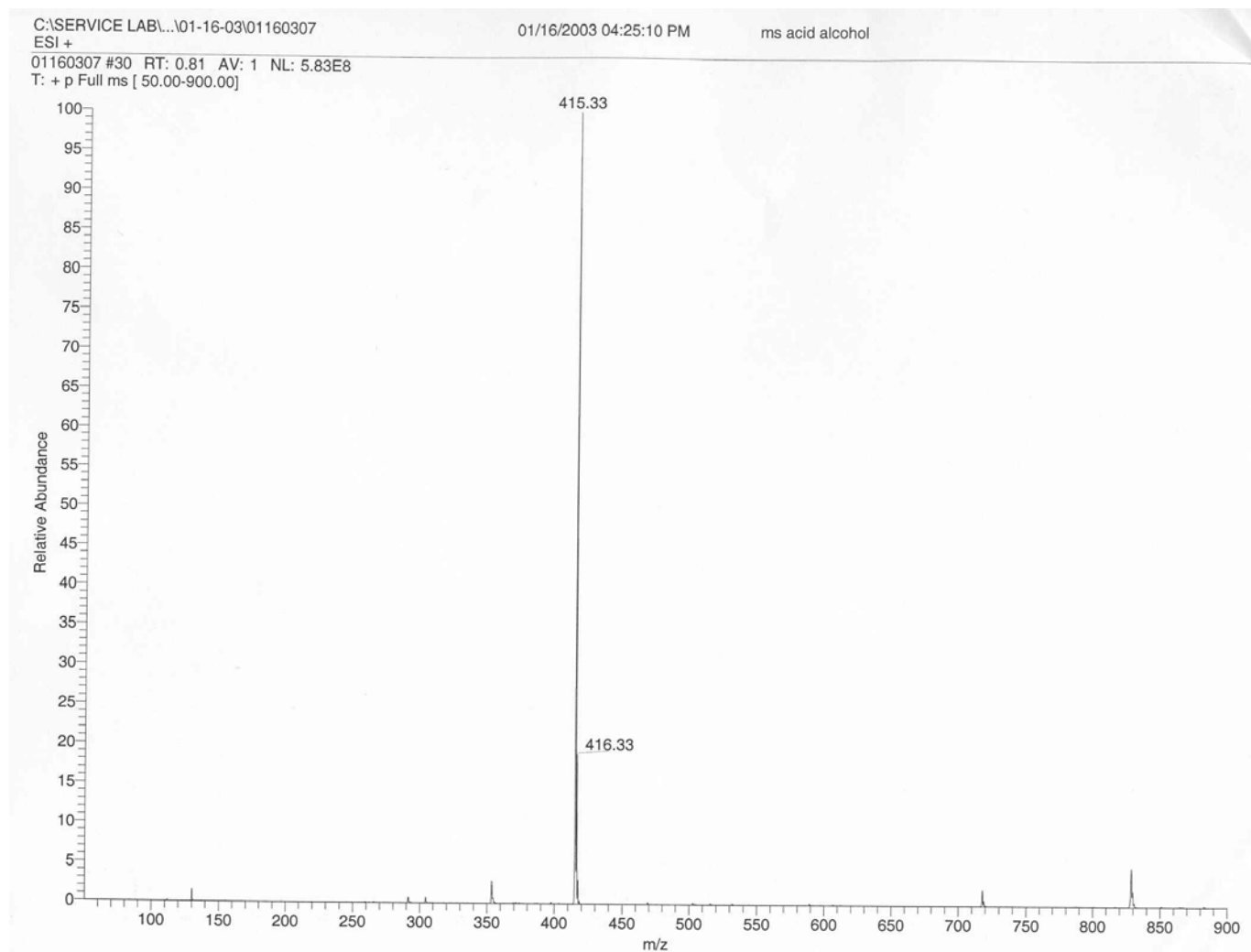




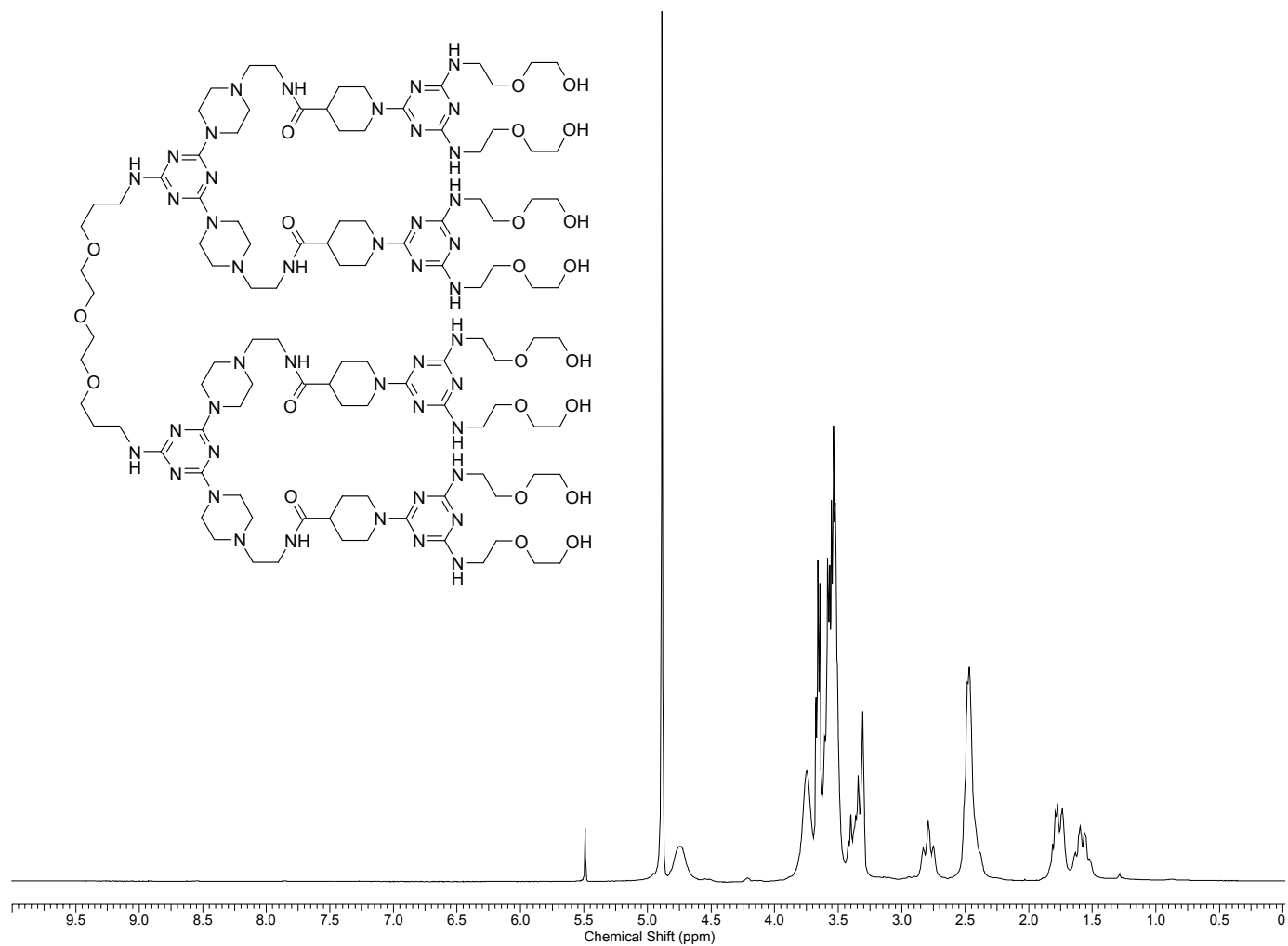
**Figure B.6a.** The <sup>1</sup>H NMR spectrum of intermediate **19**. (300 MHz, CD<sub>3</sub>OD)



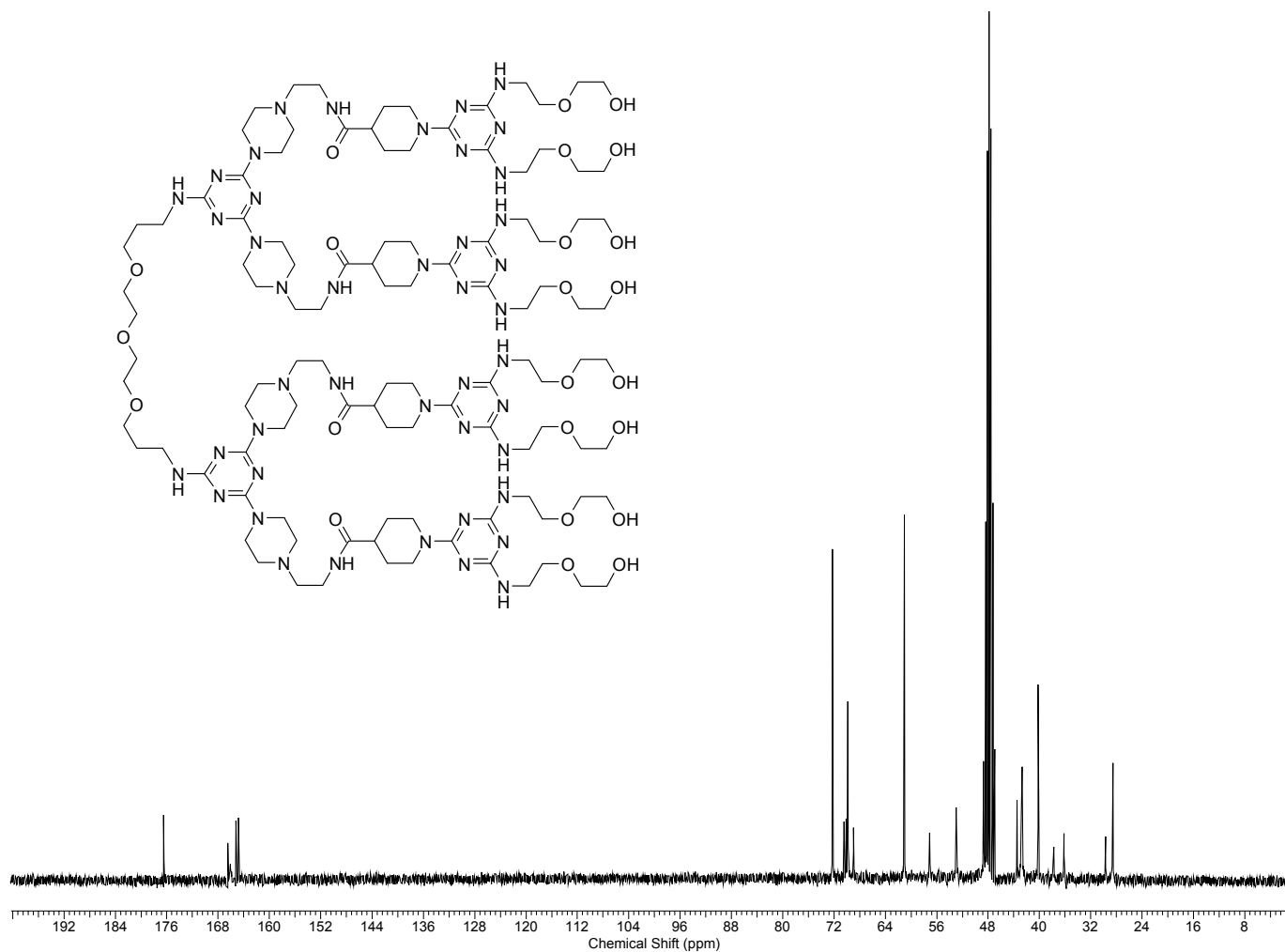
**Figure B.6b.** The  $^{13}\text{C}$  NMR spectrum of intermediate **19**. (300 MHz,  $\text{CD}_3\text{OD}$ )



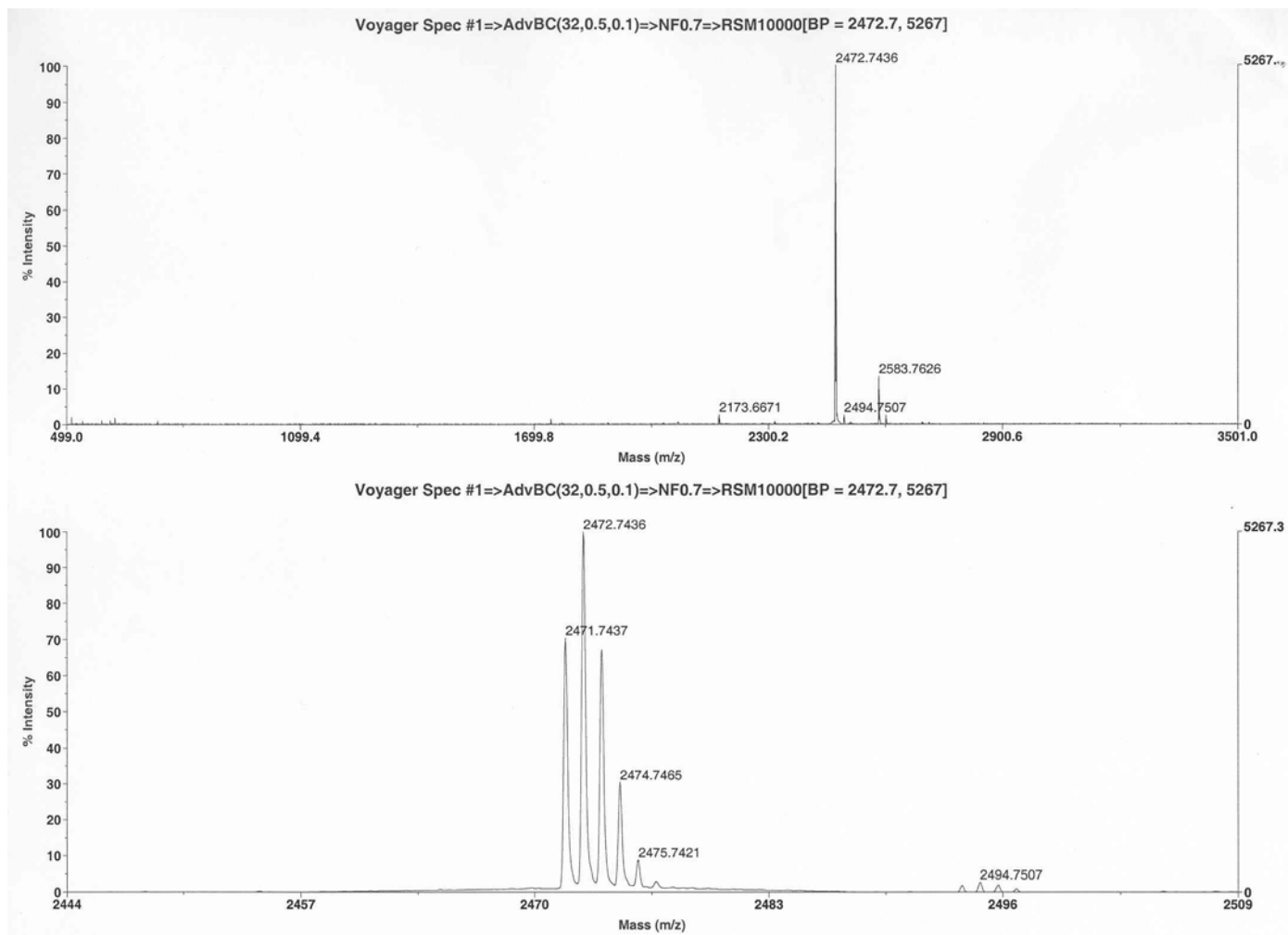
**Figure B.6c.** The ESI-TOF mass spectrum of intermediate **19**.



**Figure B.7a.** The  $^1\text{H}$  NMR spectrum of dendrimer **20**. (300 MHz,  $\text{CD}_3\text{OD}$ )

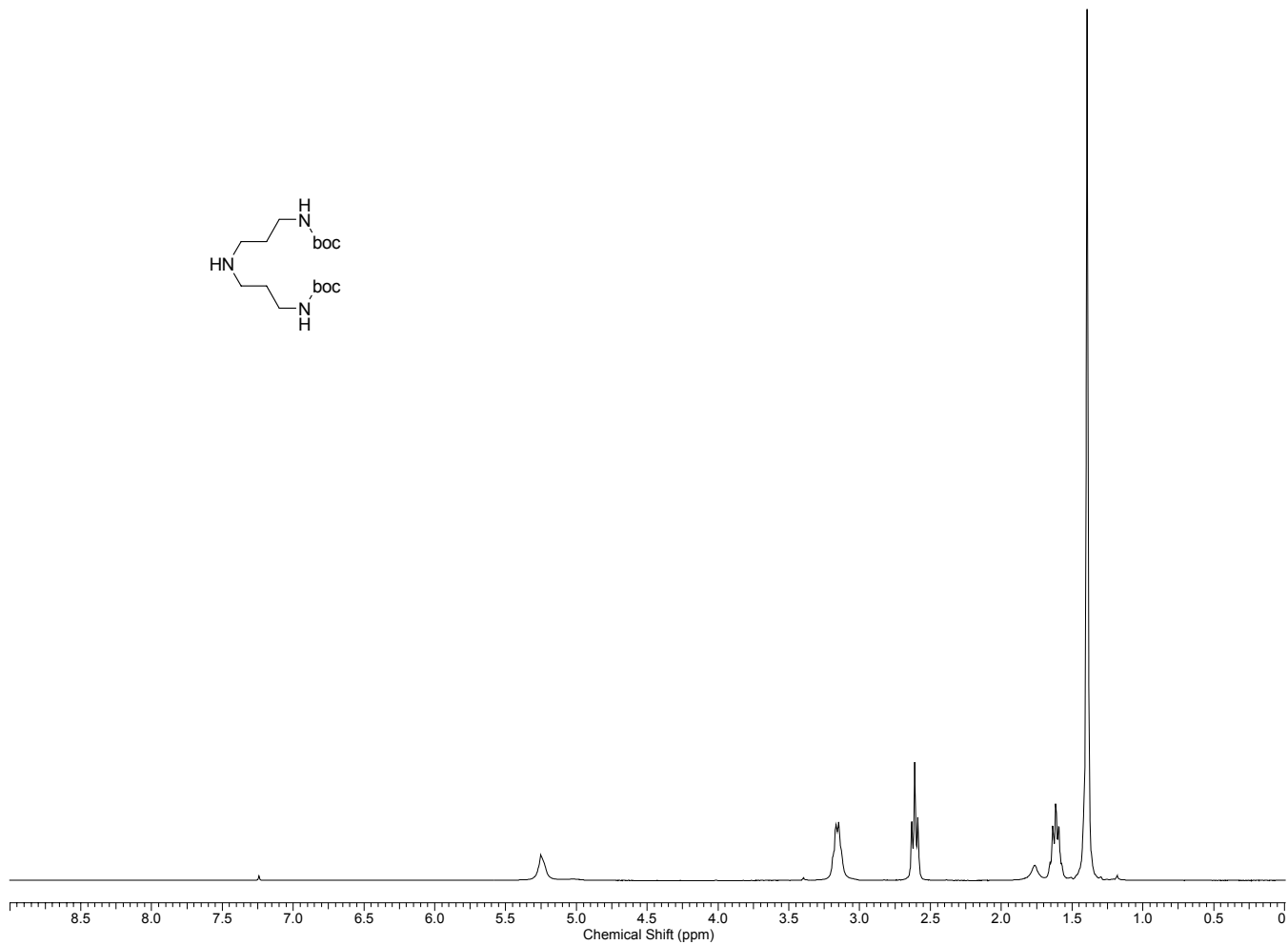


**Figure B.7b.** The  $^{13}\text{C}$  NMR spectrum of dendrimer **20**. (300 MHz,  $\text{CD}_3\text{OD}$ ).



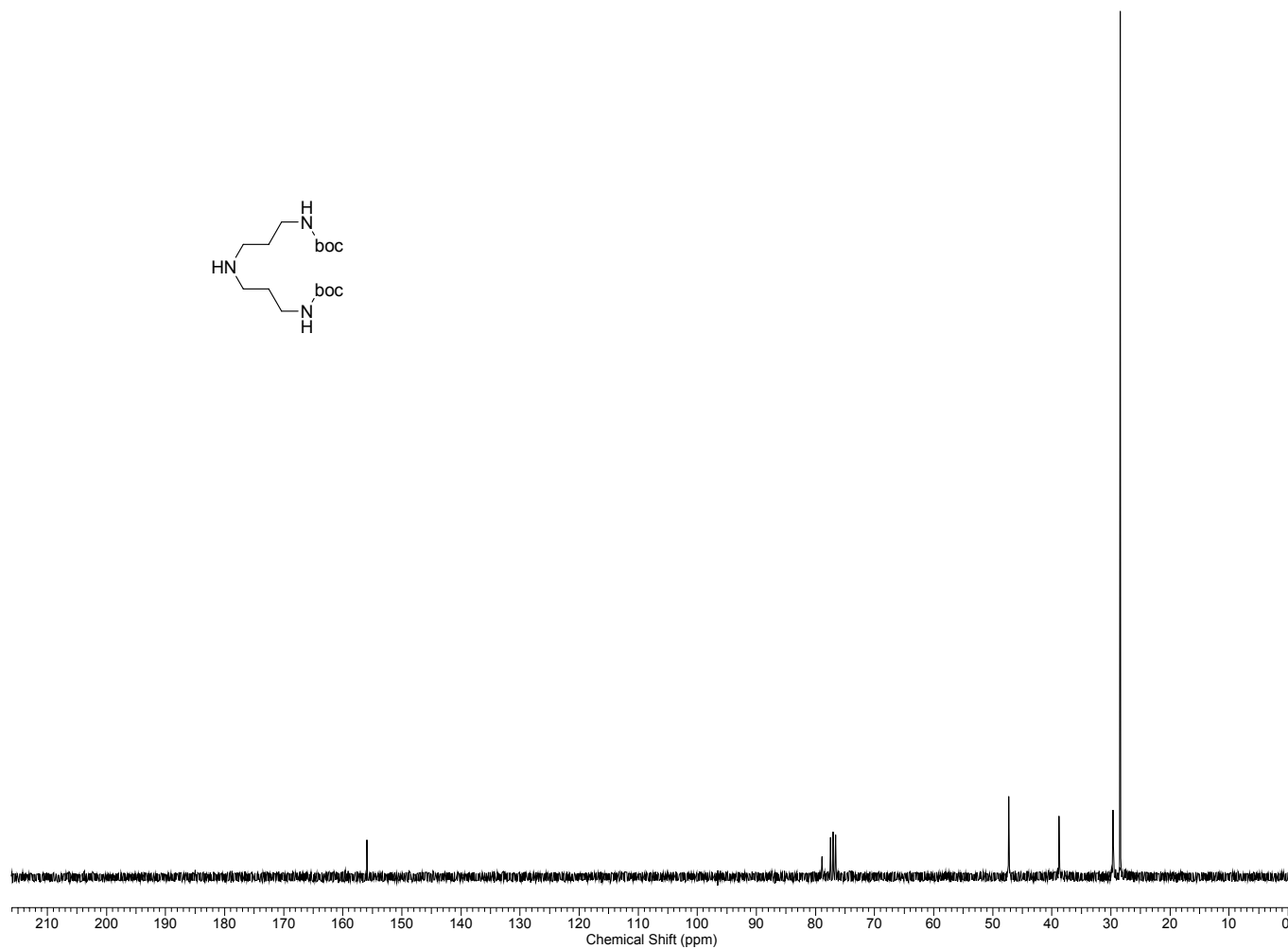
**Figure B.7c.** The MALDI-TOF mass spectrum of dendrimer **20**.

**APPENDIX C****SPECTRA RELEVANT TO CHAPTER III**



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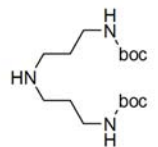


**Figure C.1b.** The <sup>13</sup>C NMR spectrum of bisBOCtriamine, **2**. (75 MHz, CDCl<sub>3</sub>)

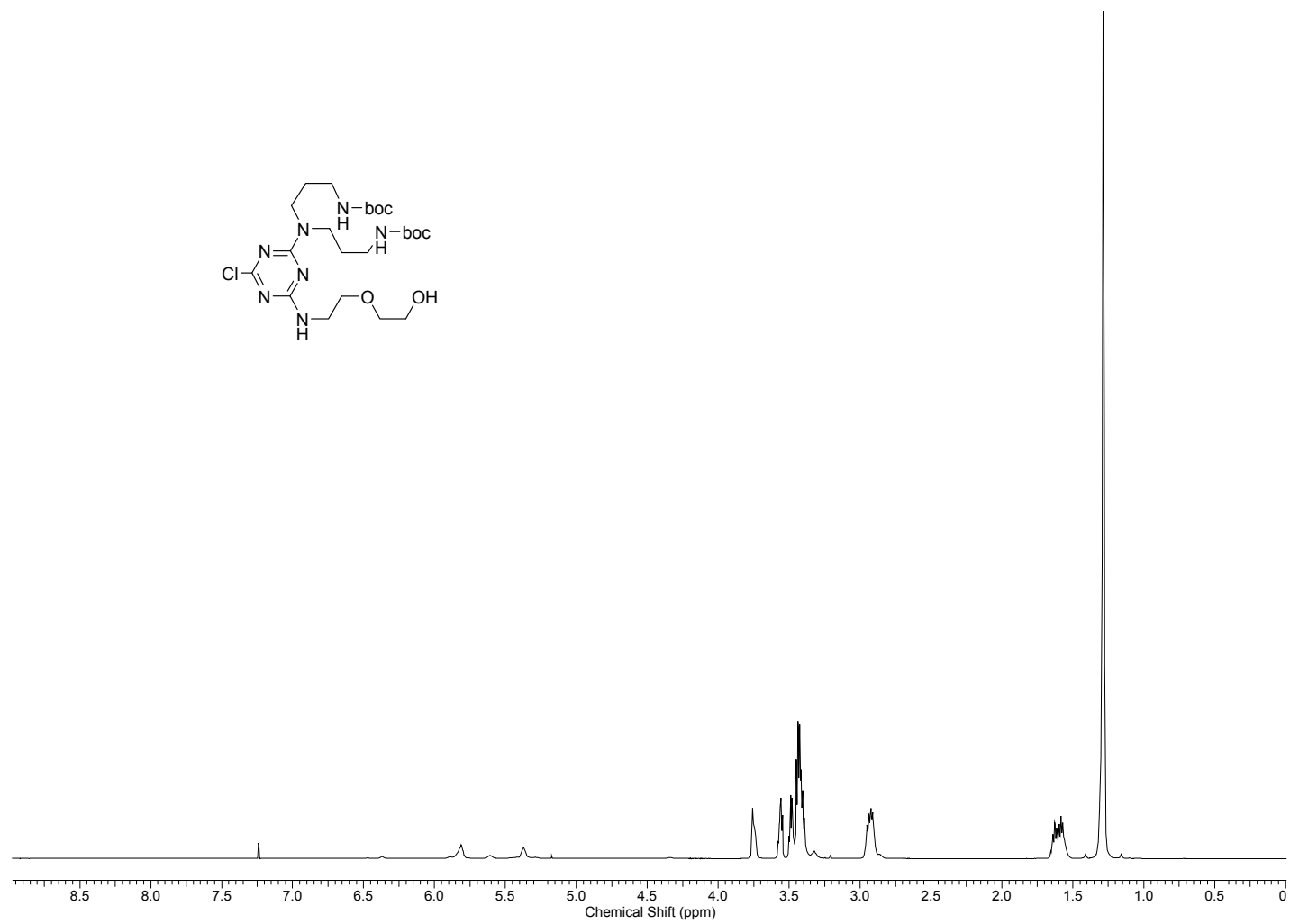
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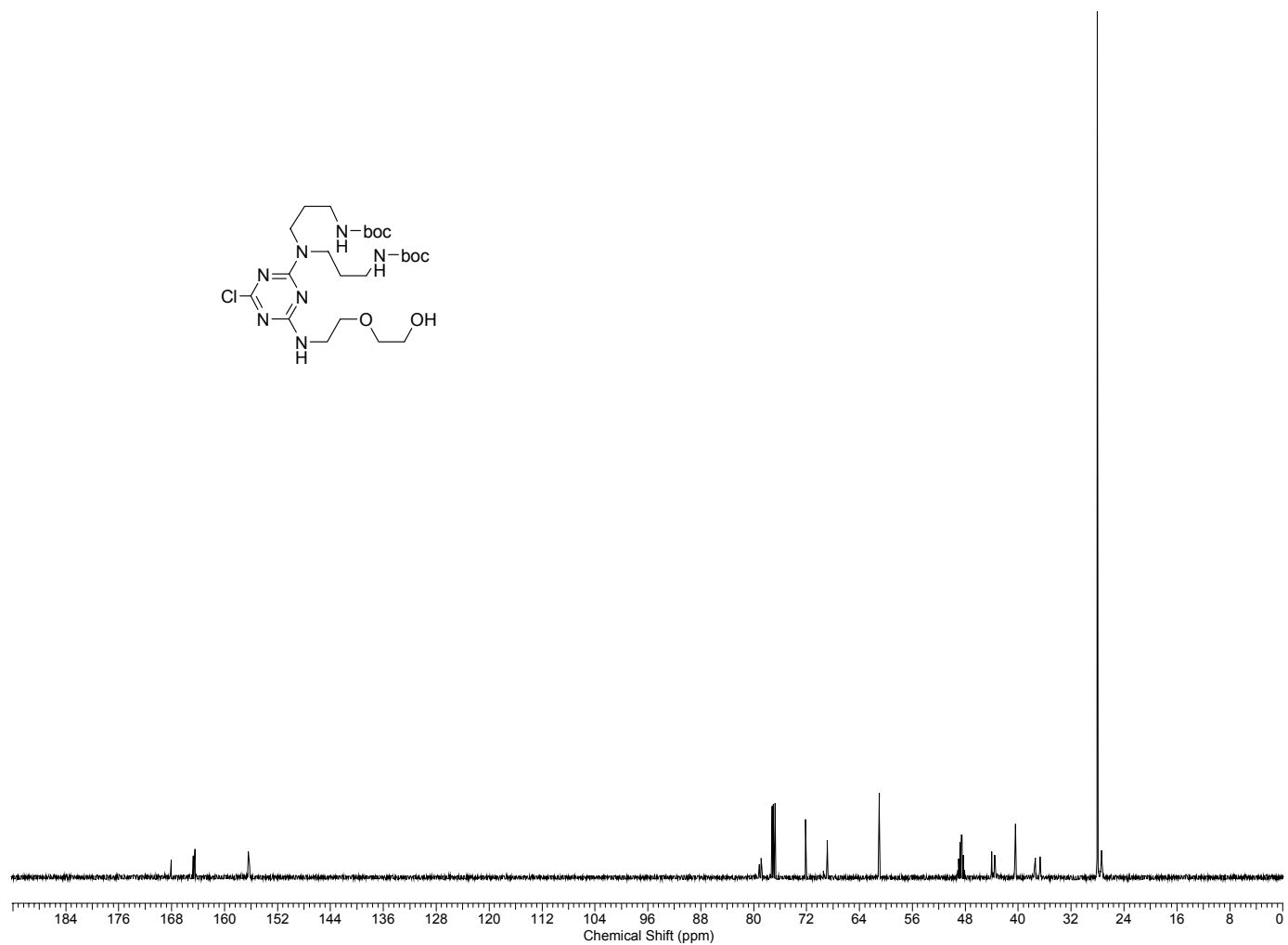
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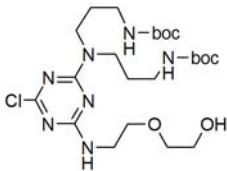
191



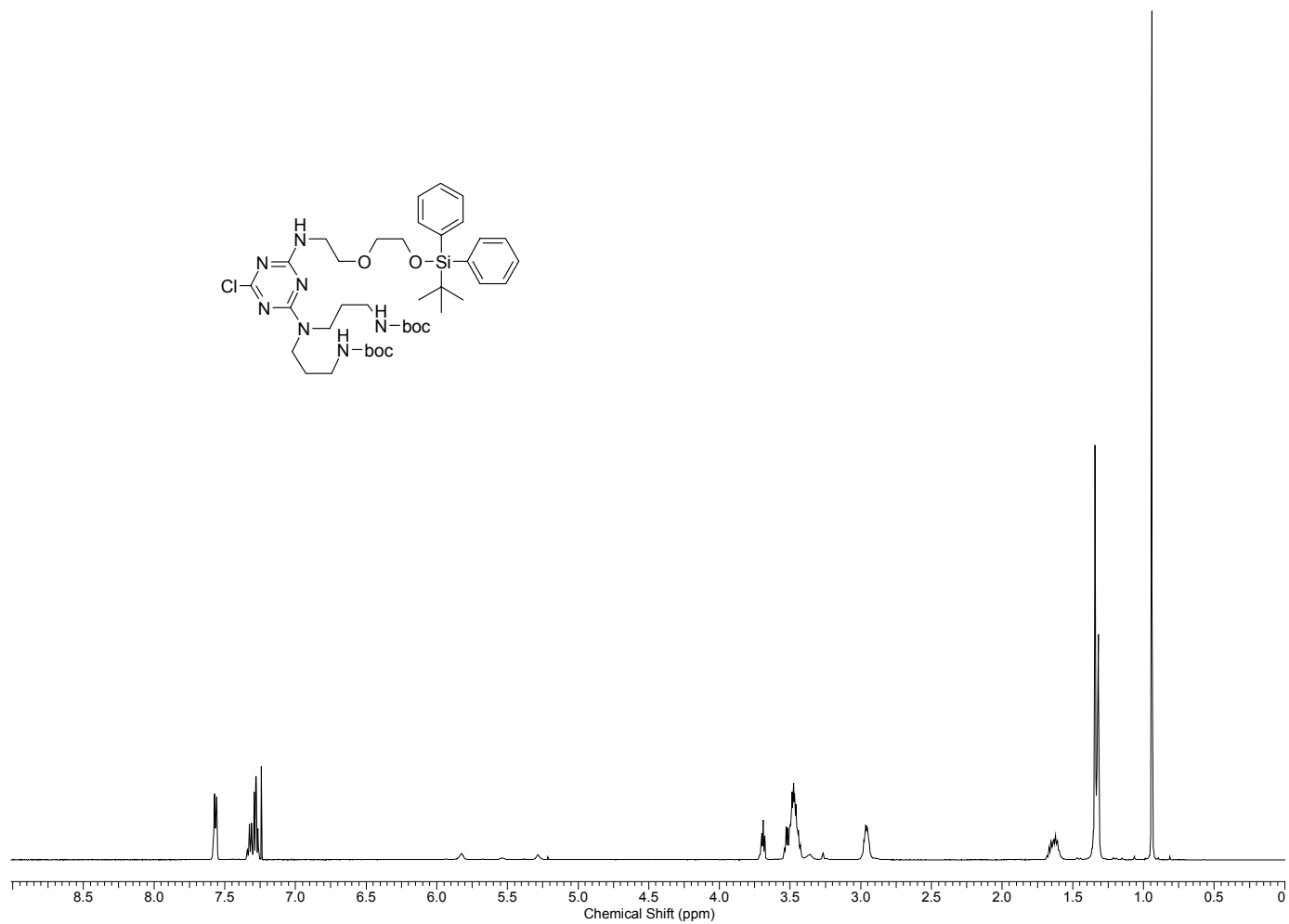
**Figure C.2a.** The  $^1\text{H}$  NMR spectrum of Free OH-Cl, **3**. (500 MHz,  $\text{CDCl}_3$ )



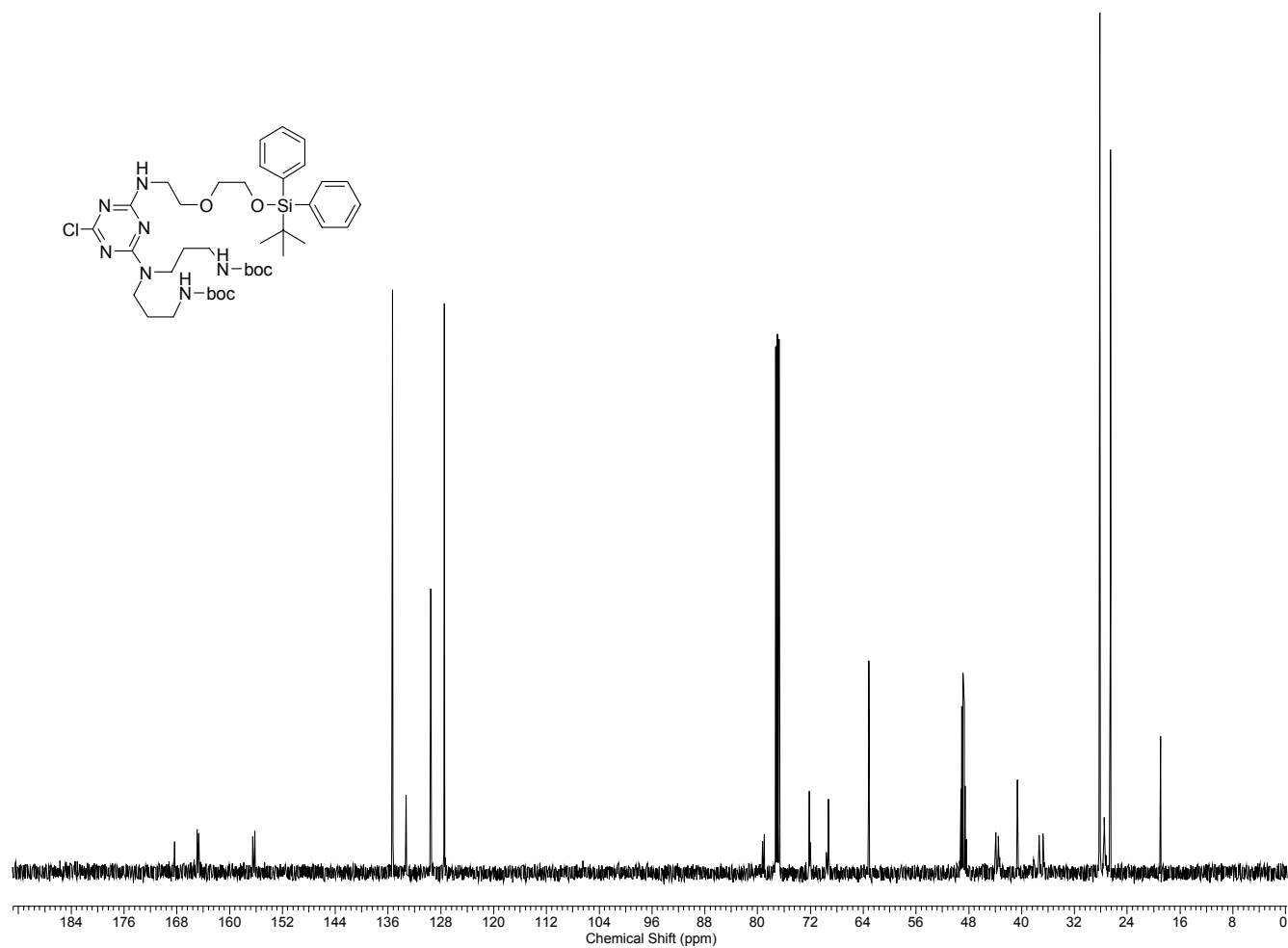
**Figure C.2b.** The  $^{13}\text{C}$  NMR spectrum of Free OH-Cl, **3**. (125 MHz,  $\text{CDCl}_3$ )



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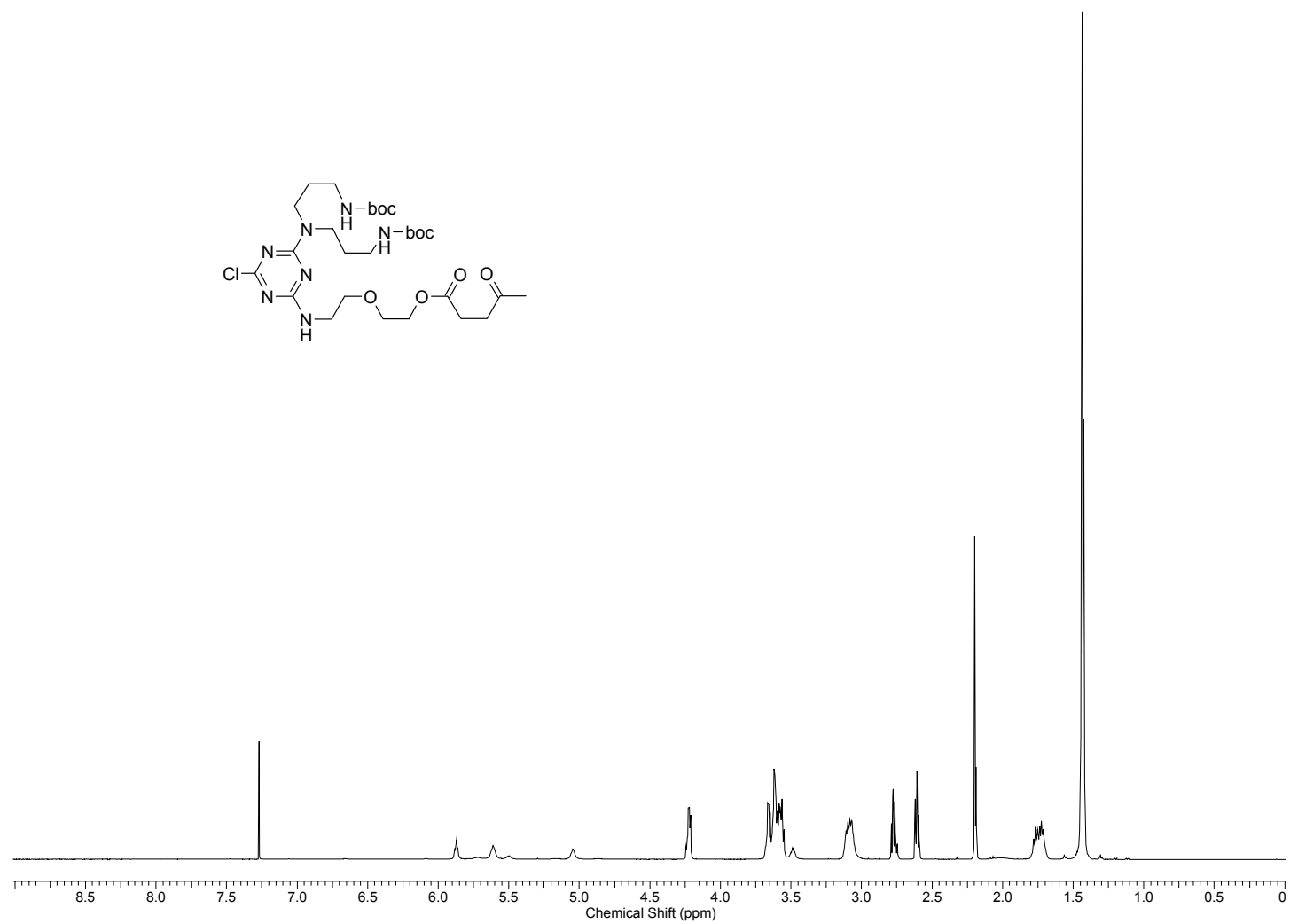
**Figure C.3a.** The <sup>1</sup>H NMR spectrum of TBDPS-Cl, **4**. (500 MHz, CDCl<sub>3</sub>)



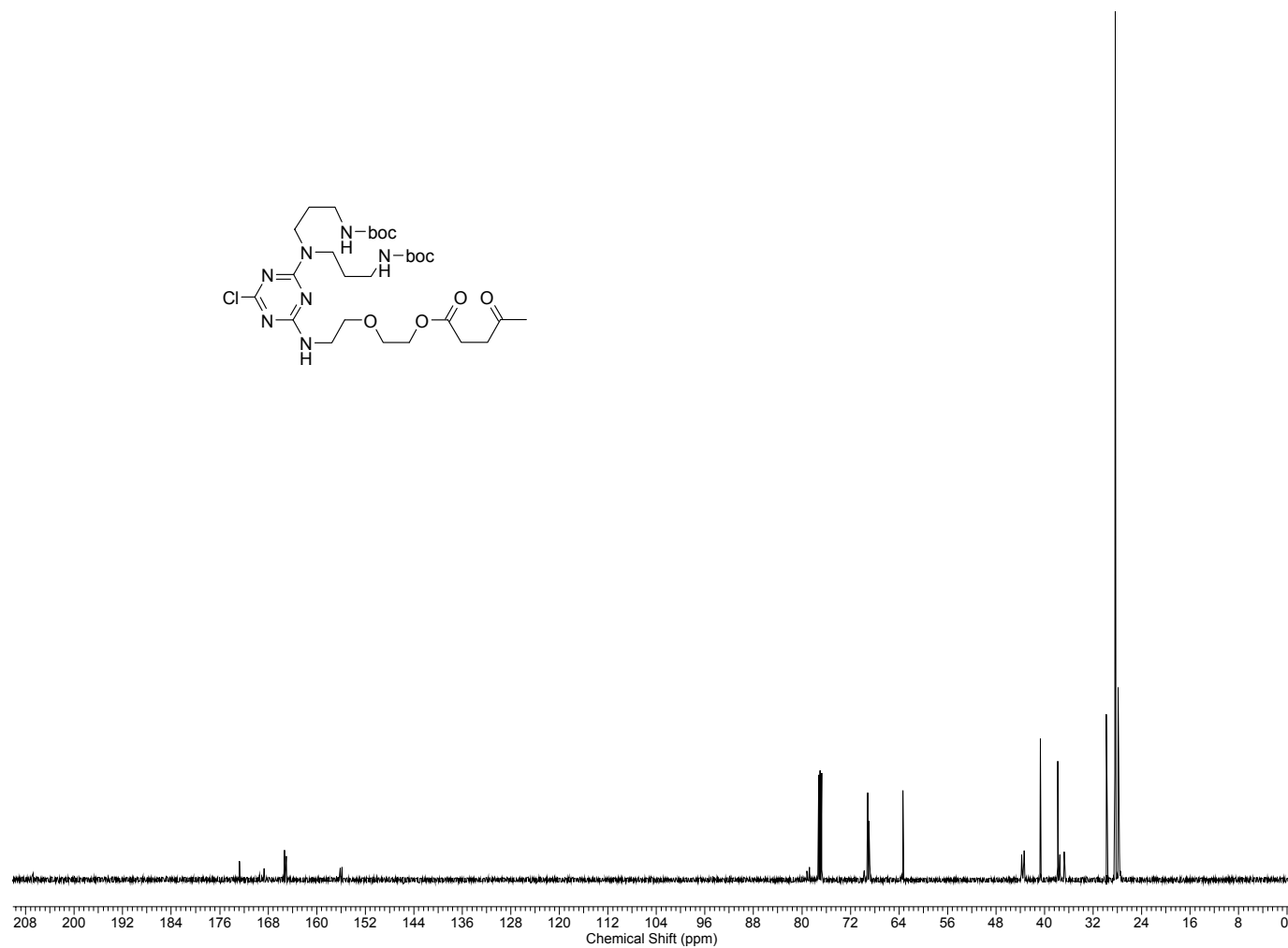
**Figure C.3b.** The  $^{13}\text{C}$  NMR spectrum of TBDPS-Cl, 4. (125 MHz,  $\text{CDCl}_3$ )



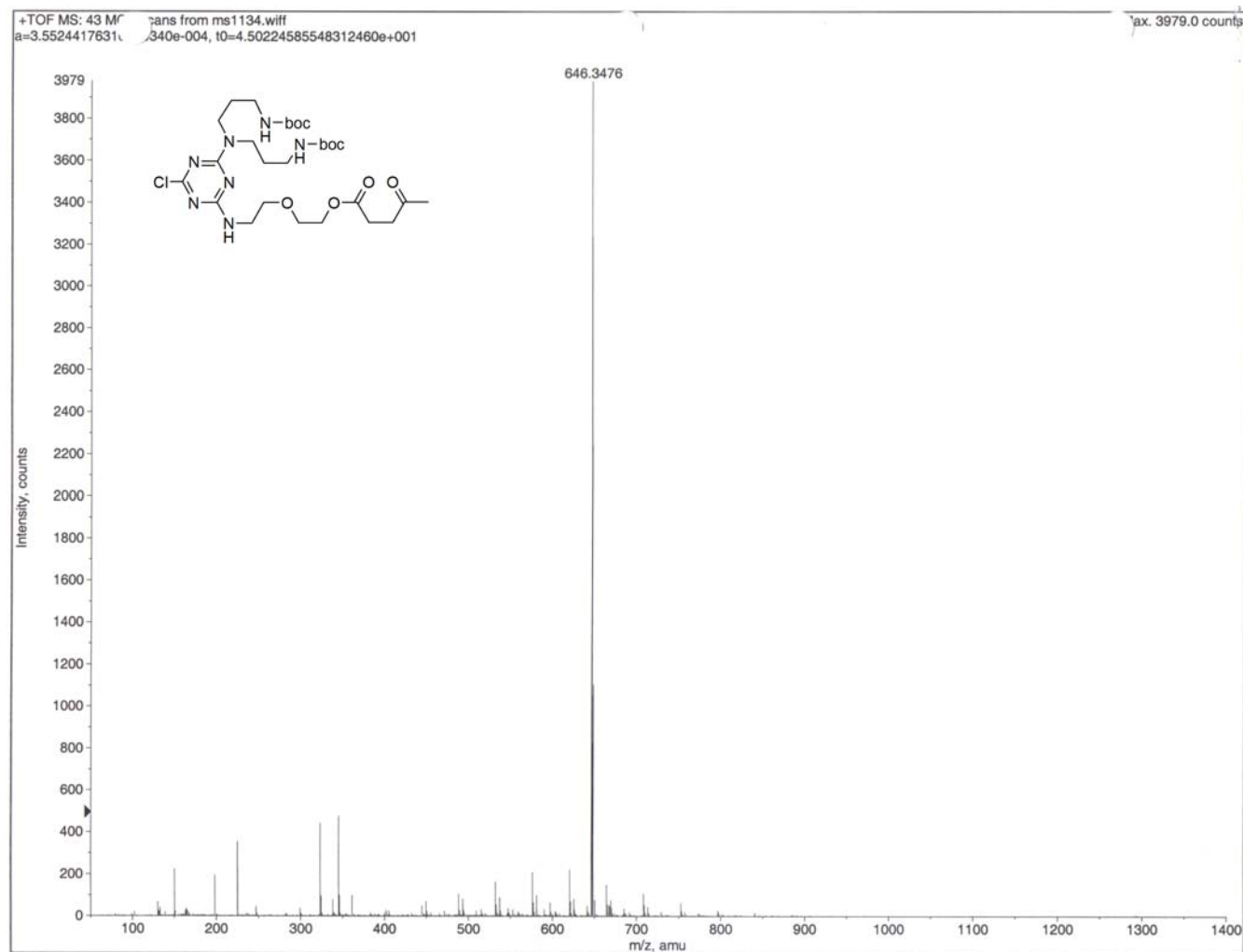




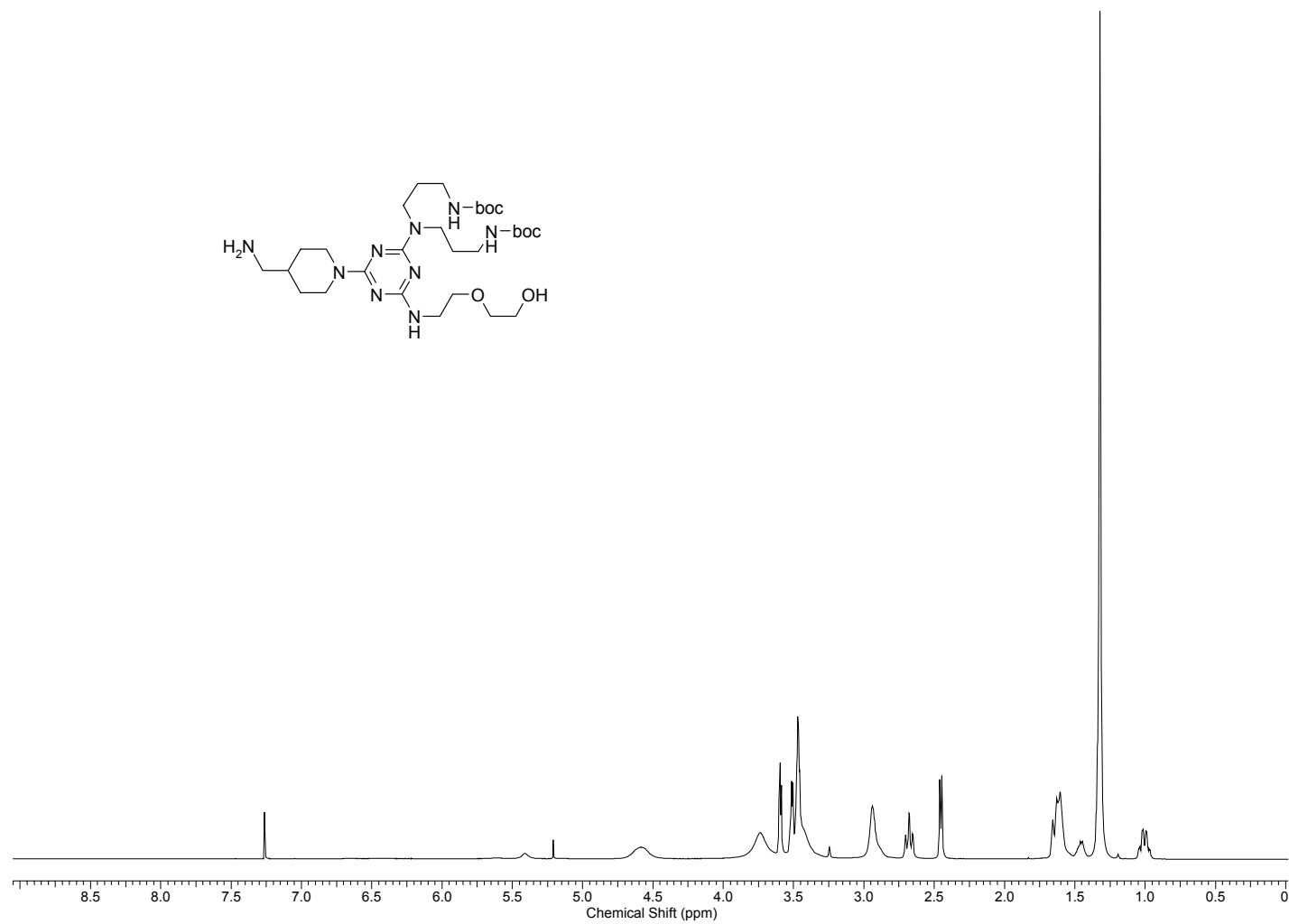
**Figure C.4a.** The <sup>1</sup>H NMR spectrum of Lev-Cl, **5**. (500 MHz, CDCl<sub>3</sub>)



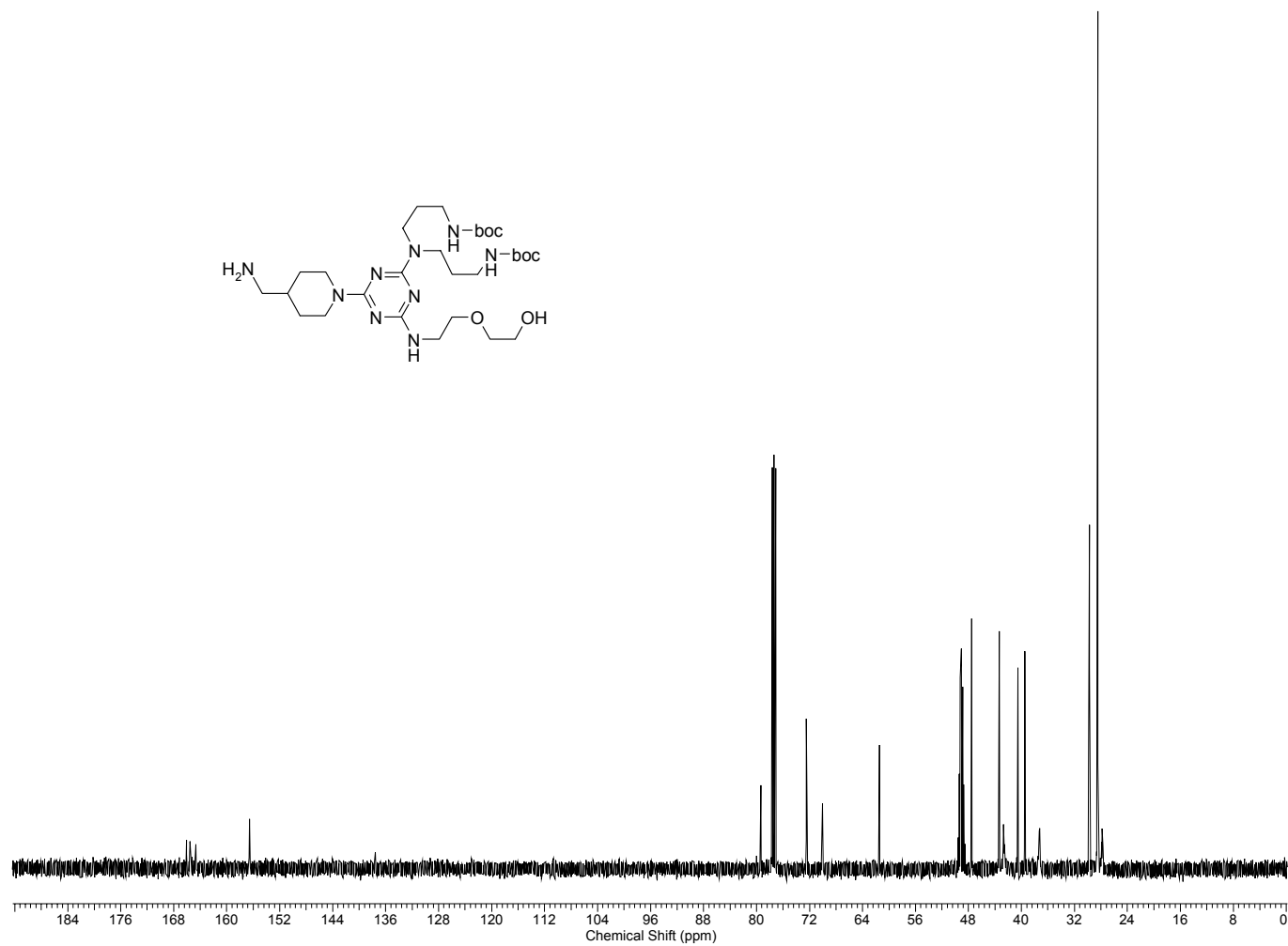
**Figure C.4b.** The <sup>13</sup>C NMR spectrum of Lev-Cl, 5. (125 MHz, CDCl<sub>3</sub>)



**Figure C.4c.** The ESI-TOF mass spectrum of Lev-Cl, **5**.



**Figure C.5a.** The <sup>1</sup>H NMR spectrum of Free OH-AMP, **6** (500 MHz, CDCl<sub>3</sub>)



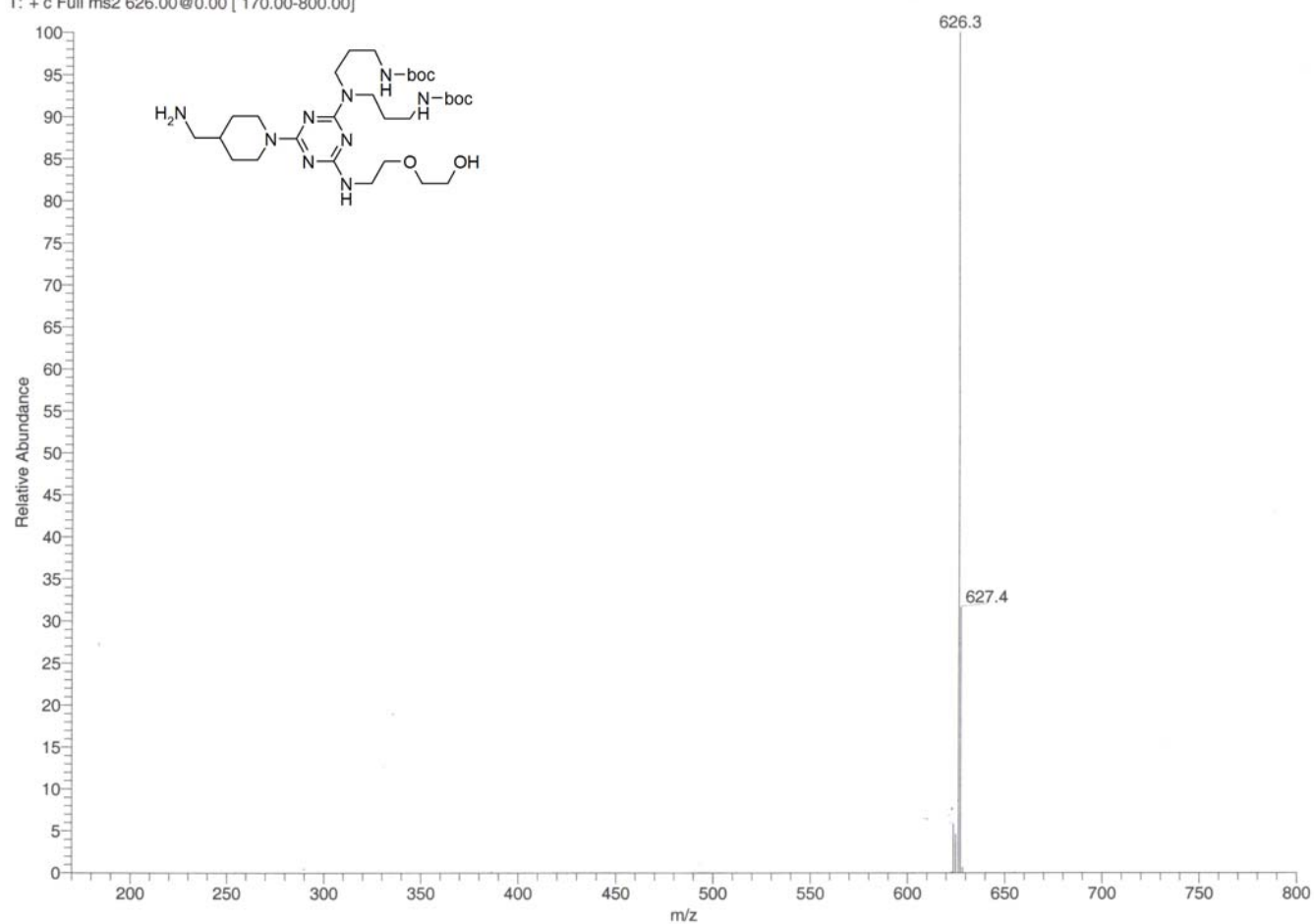
**Figure C.5b** The <sup>13</sup>C NMR spectrum of Free OH-AMP, **6** (125 MHz, CDCl<sub>3</sub>)

C:\service lab\12-22-03\MSFreeOHAMP\_2  
APCI

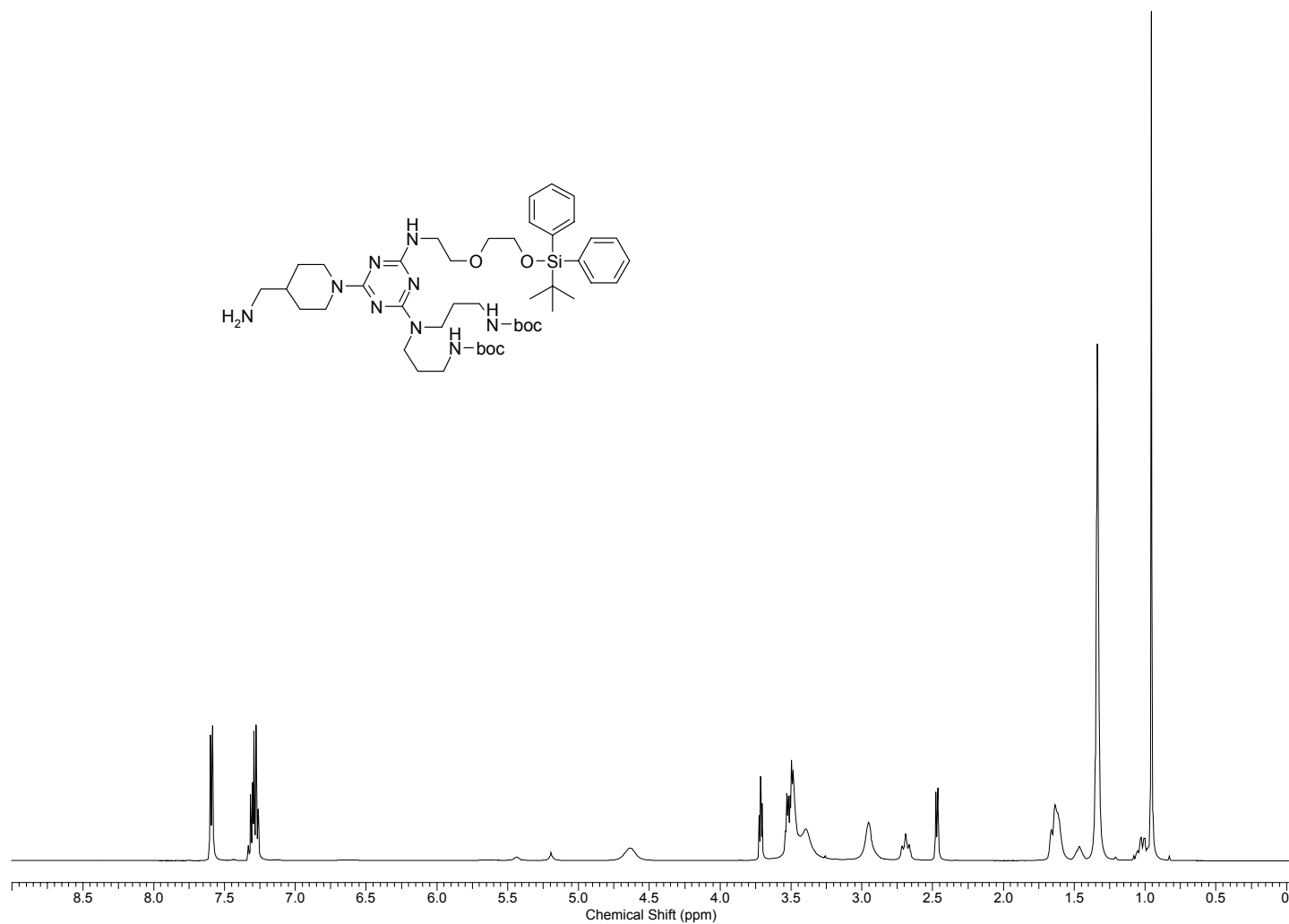
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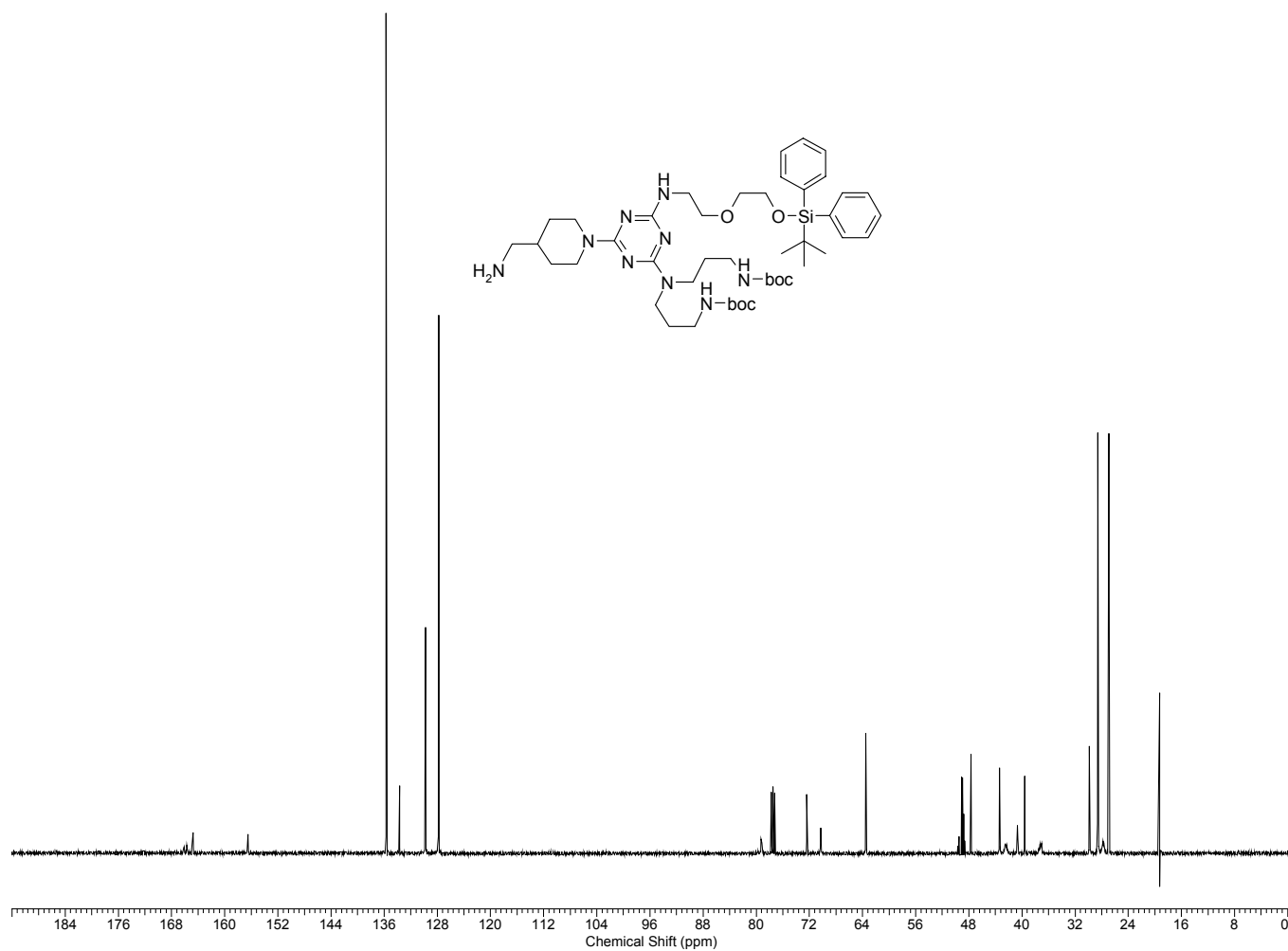
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**Figure C.5c.** The ESI-TOF mass spectrum of Free OH-AMP, **6**.

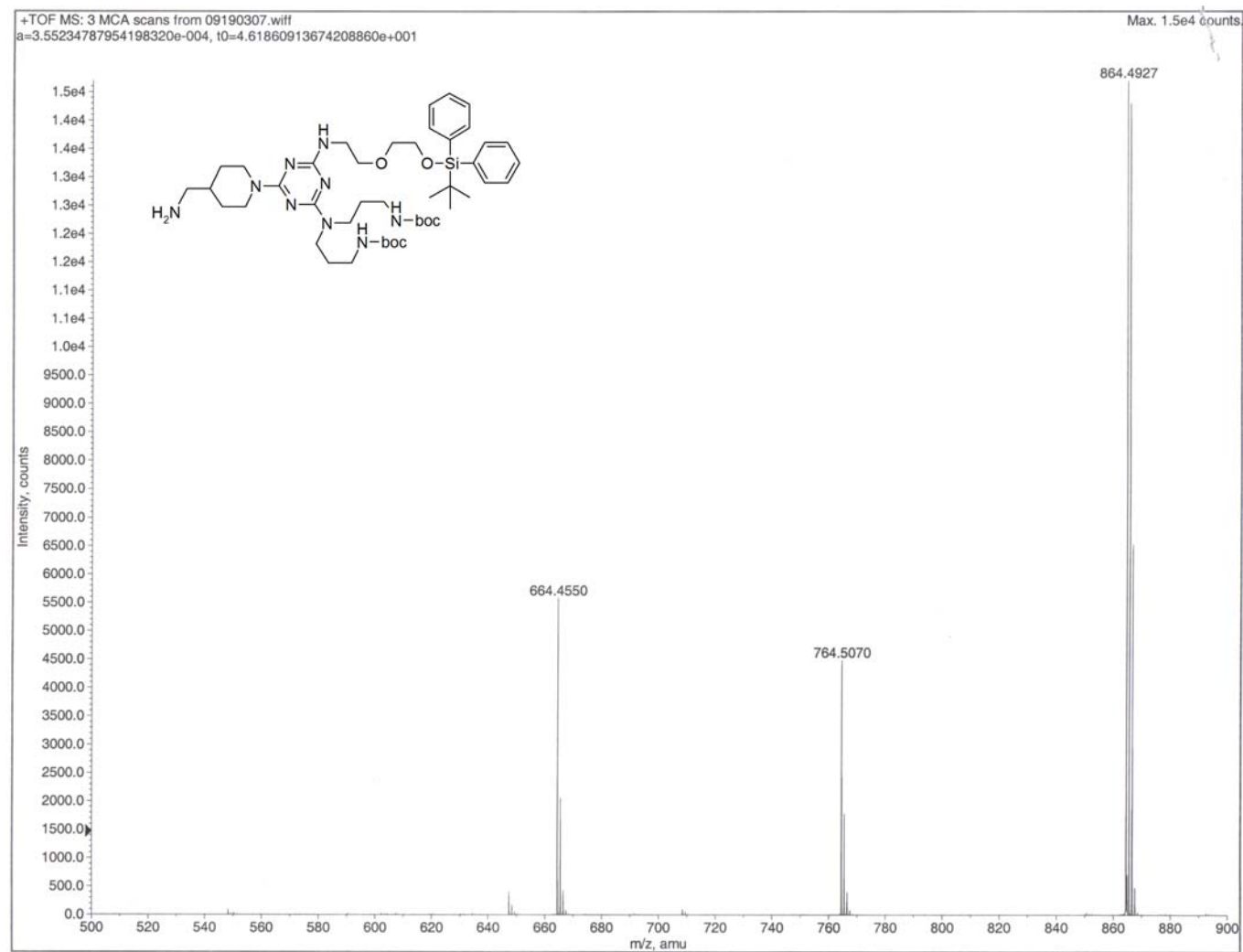


**Figure C.6a.** The  $^1\text{H}$  NMR spectrum of TBDPS-AMP, 7. (500 MHz,  $\text{CDCl}_3$ )

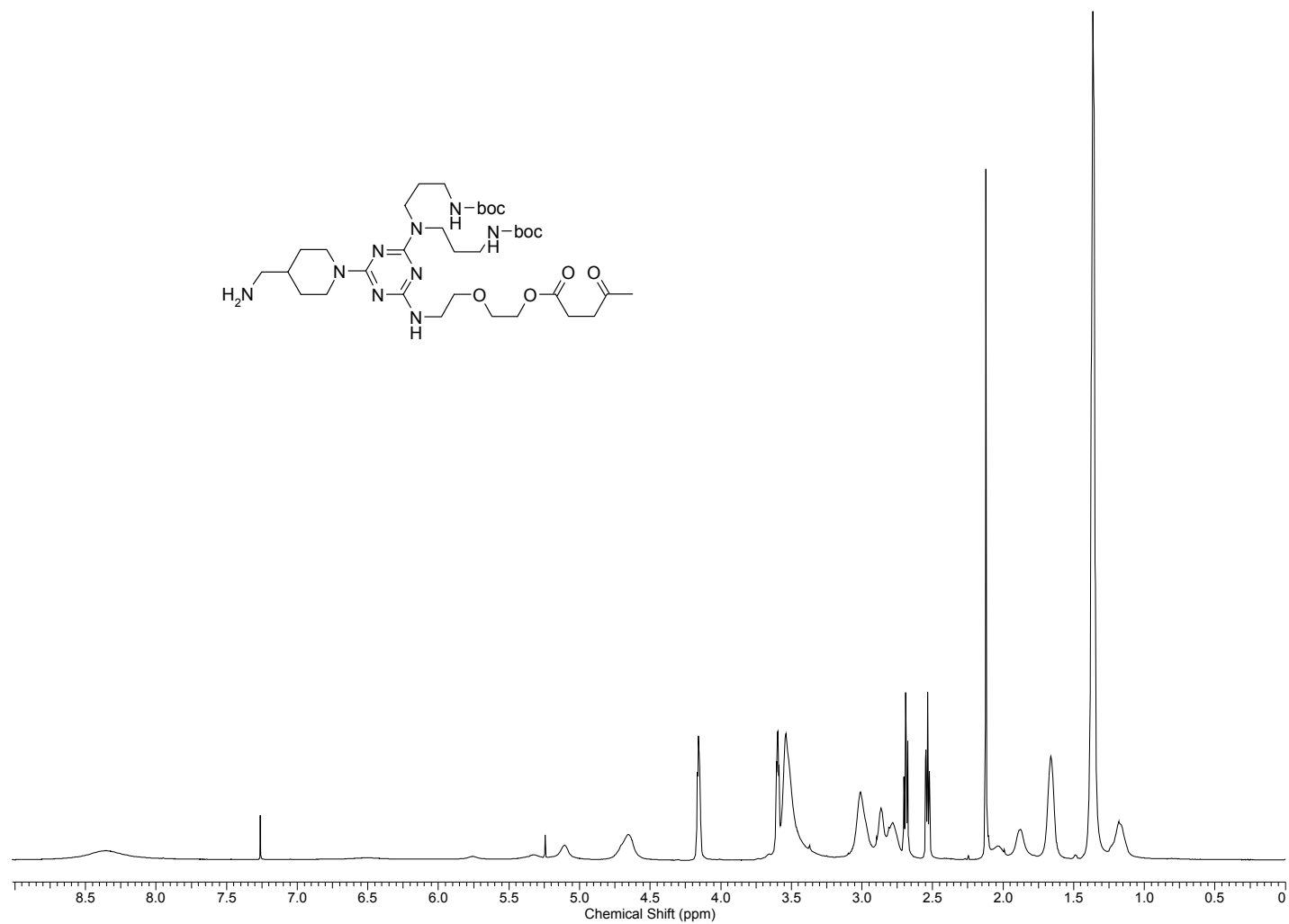


**Figure C.6b.** The  $^{13}\text{C}$  NMR spectrum of TBDPS-AMP, 7. (125 MHz,  $\text{CDCl}_3$ )

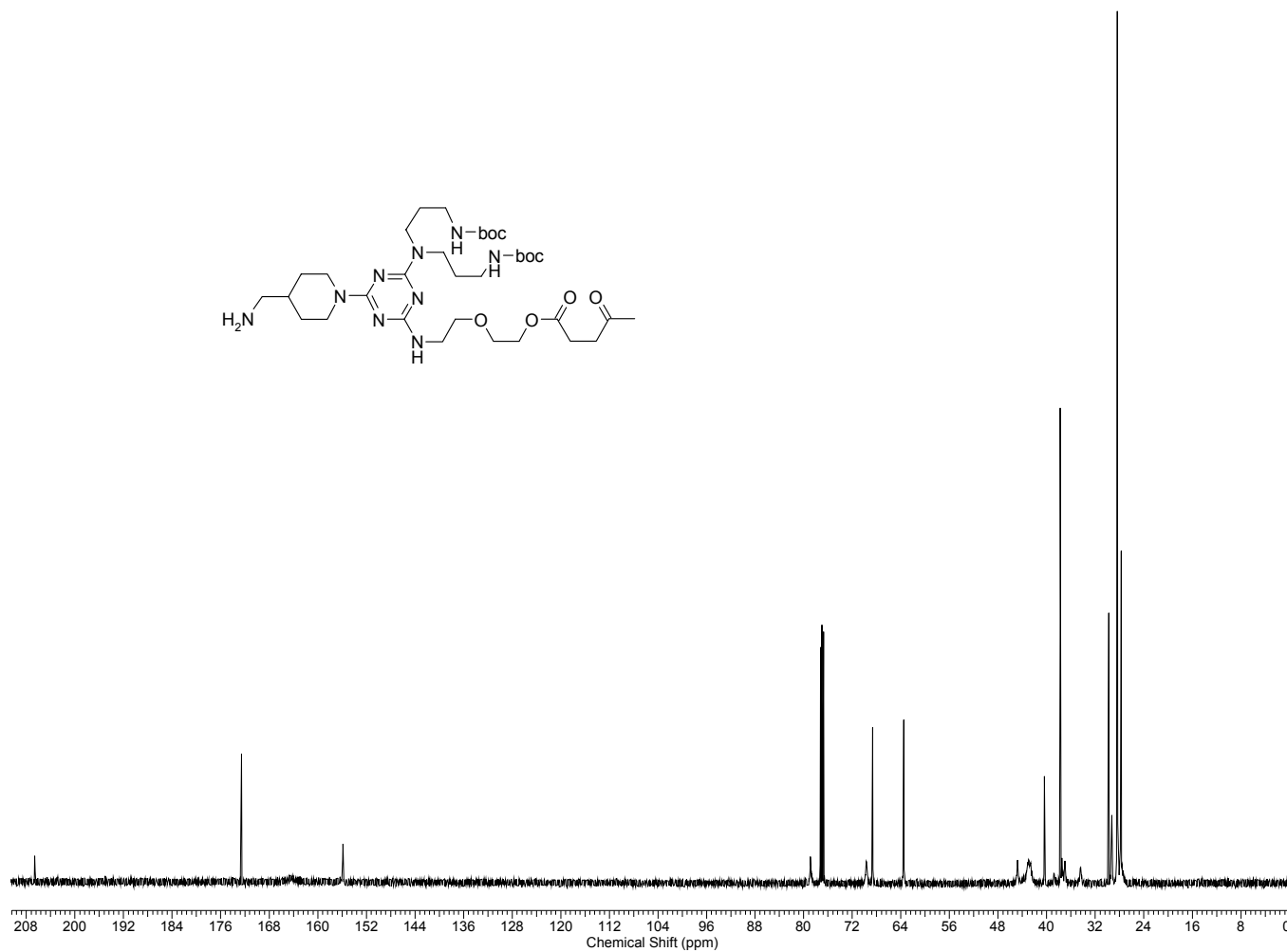




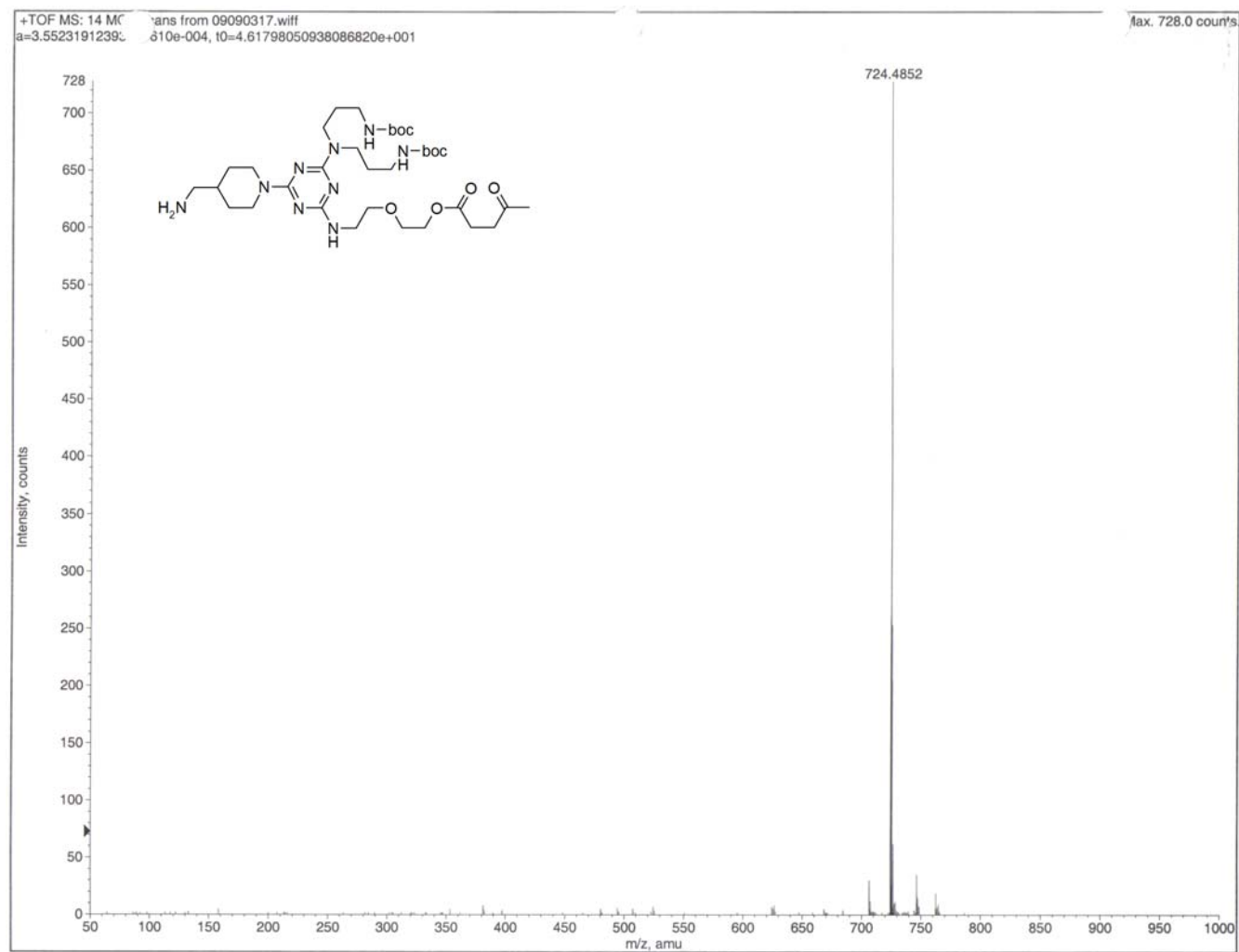
**Figure C.6c.** The ESI-TOF mass spectrum of TBDPS-AMP, **7**.



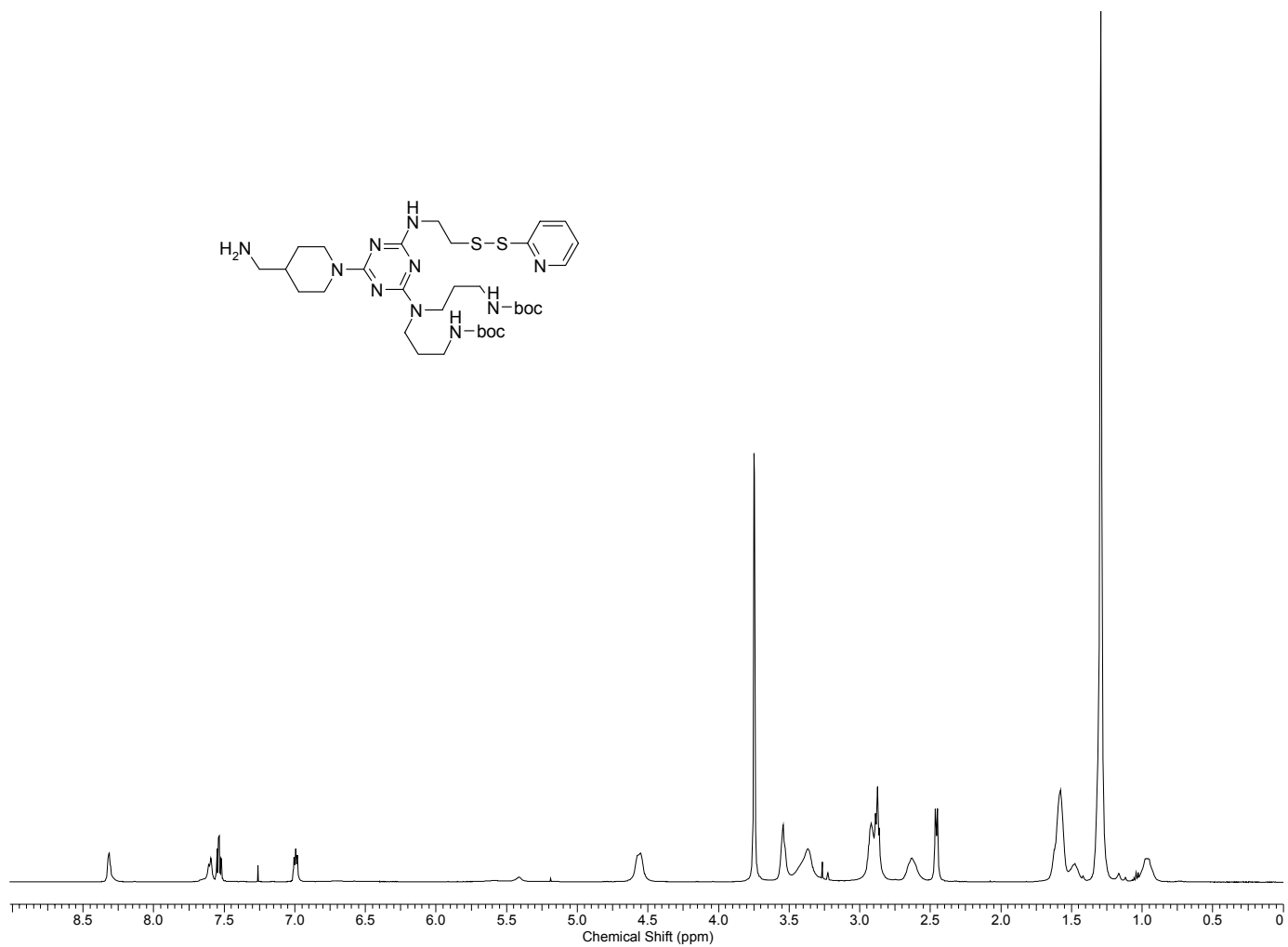
**Figure C.7a.** The <sup>1</sup>H NMR spectrum of Lev-AMP, **8**. (500 MHz, CDCl<sub>3</sub>)



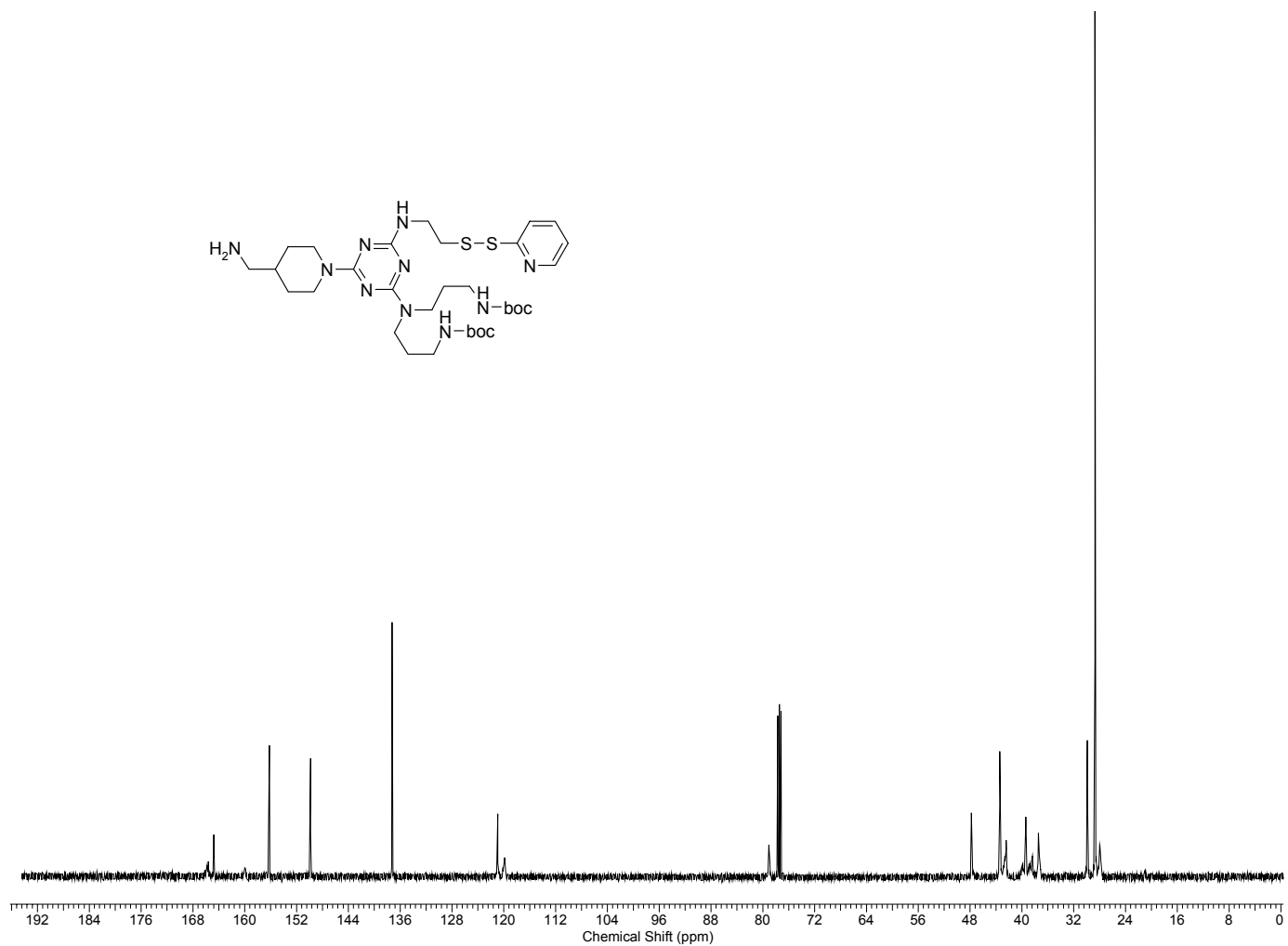
**Figure C.7b.** The  $^{13}\text{C}$  NMR spectrum of Lev-AMP, **8**. (125 MHz,  $\text{CDCl}_3$ )



**Figure C.7c.** The ESI-TOF mass spectrum of Lev-AMP, **8**.

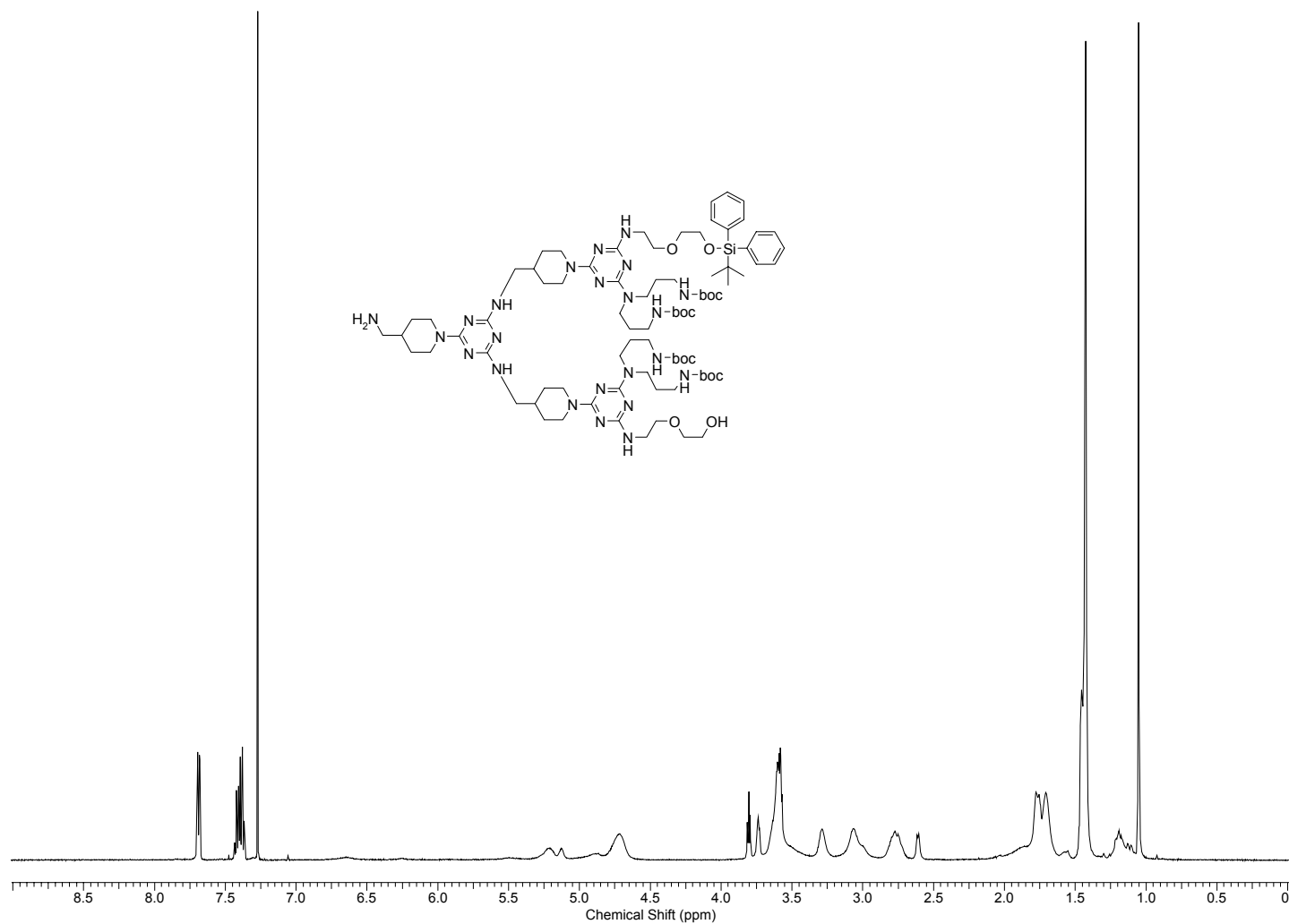


**Figure C.8a.** The <sup>1</sup>H NMR spectrum of Pyr-Amp, **9**. (500 MHz, CDCl<sub>3</sub>)



**Figure C.8b.** The  $^{13}\text{C}$  NMR spectrum of Pyr-Amp, **9**. (125 MHz,  $\text{CDCl}_3$ )

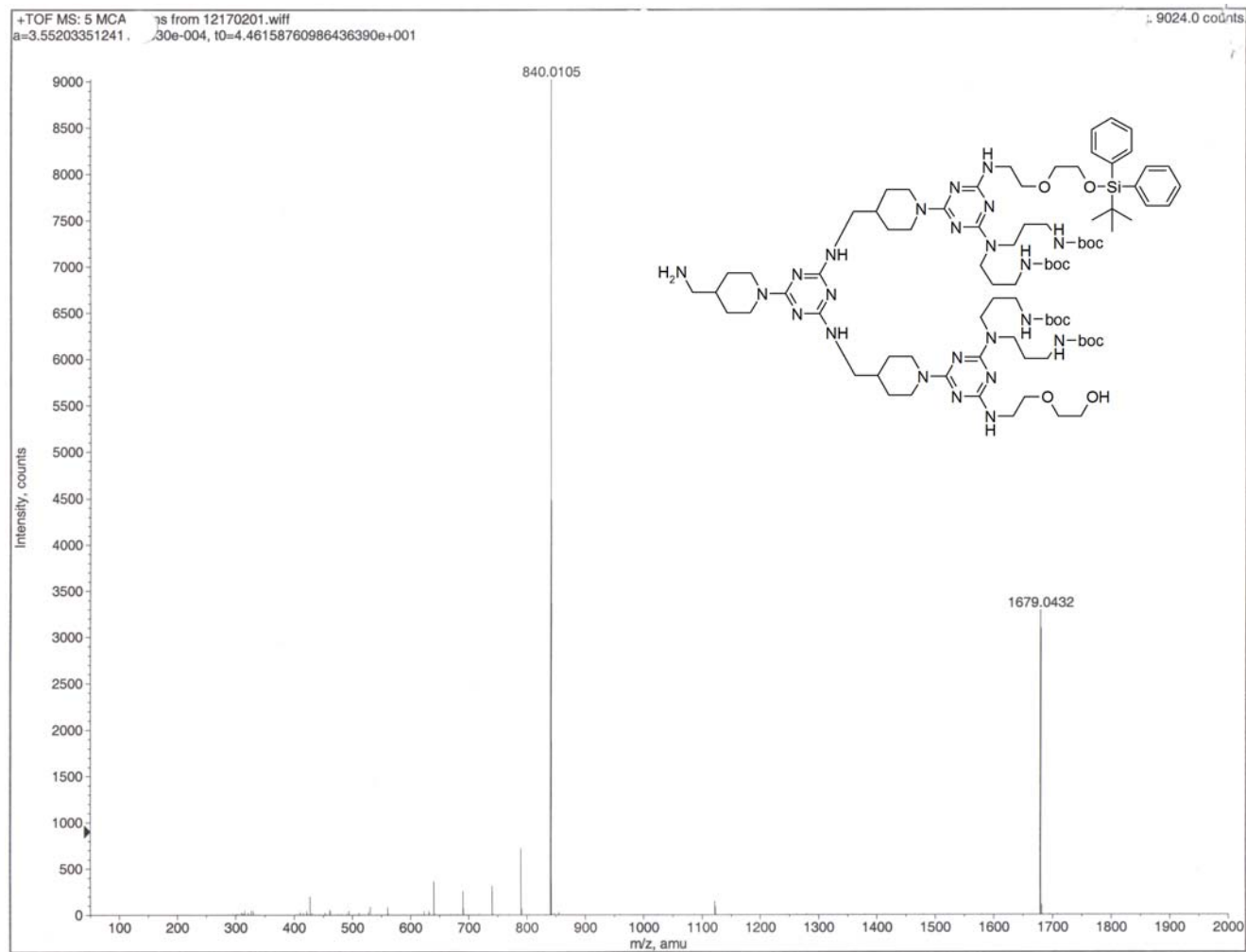




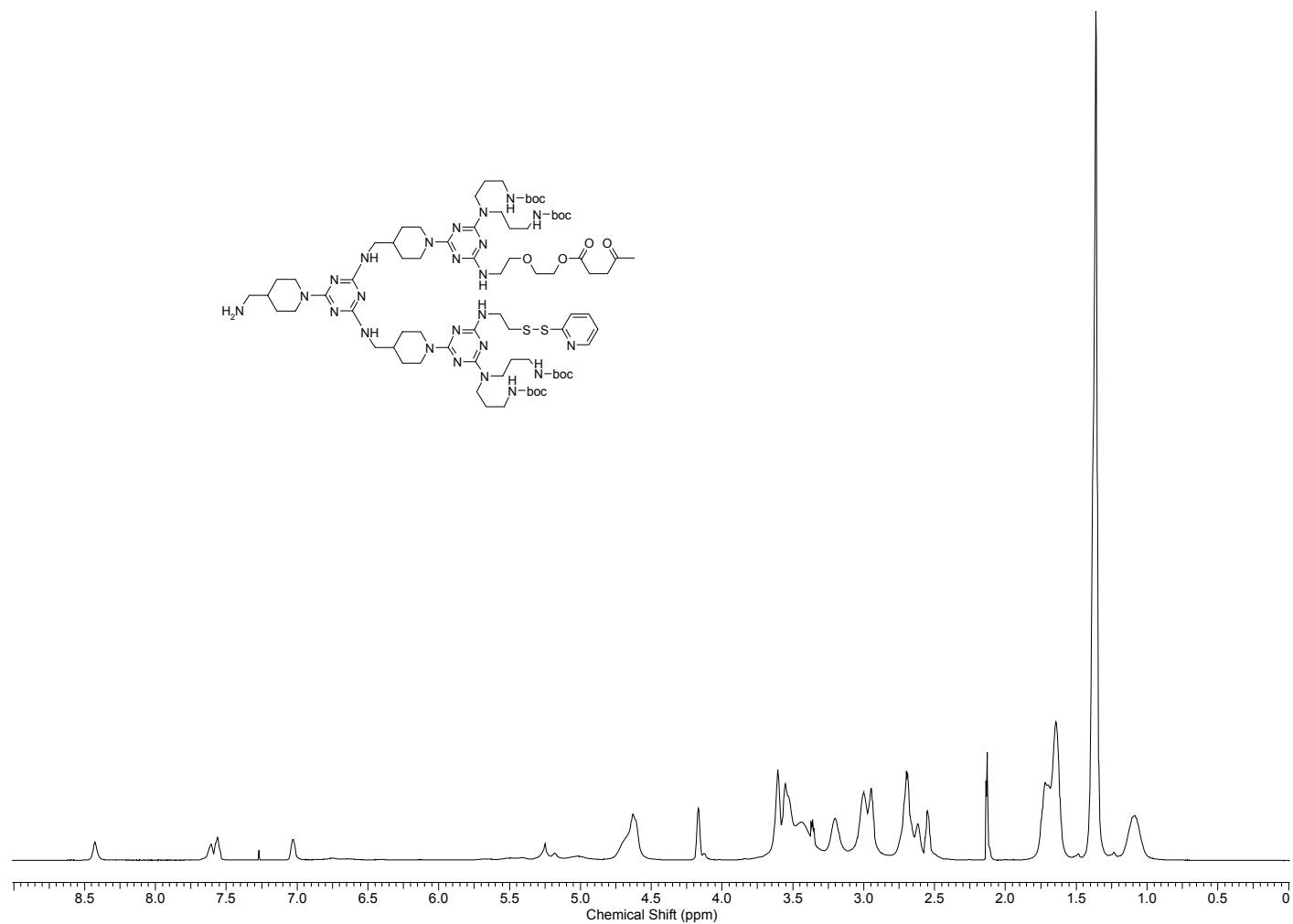
**Figure C.9a.** The  $^1\text{H}$  NMR spectrum of TBDPS-Free OH-AMP, **10**. (500 MHz,  $\text{CDCl}_3$ )



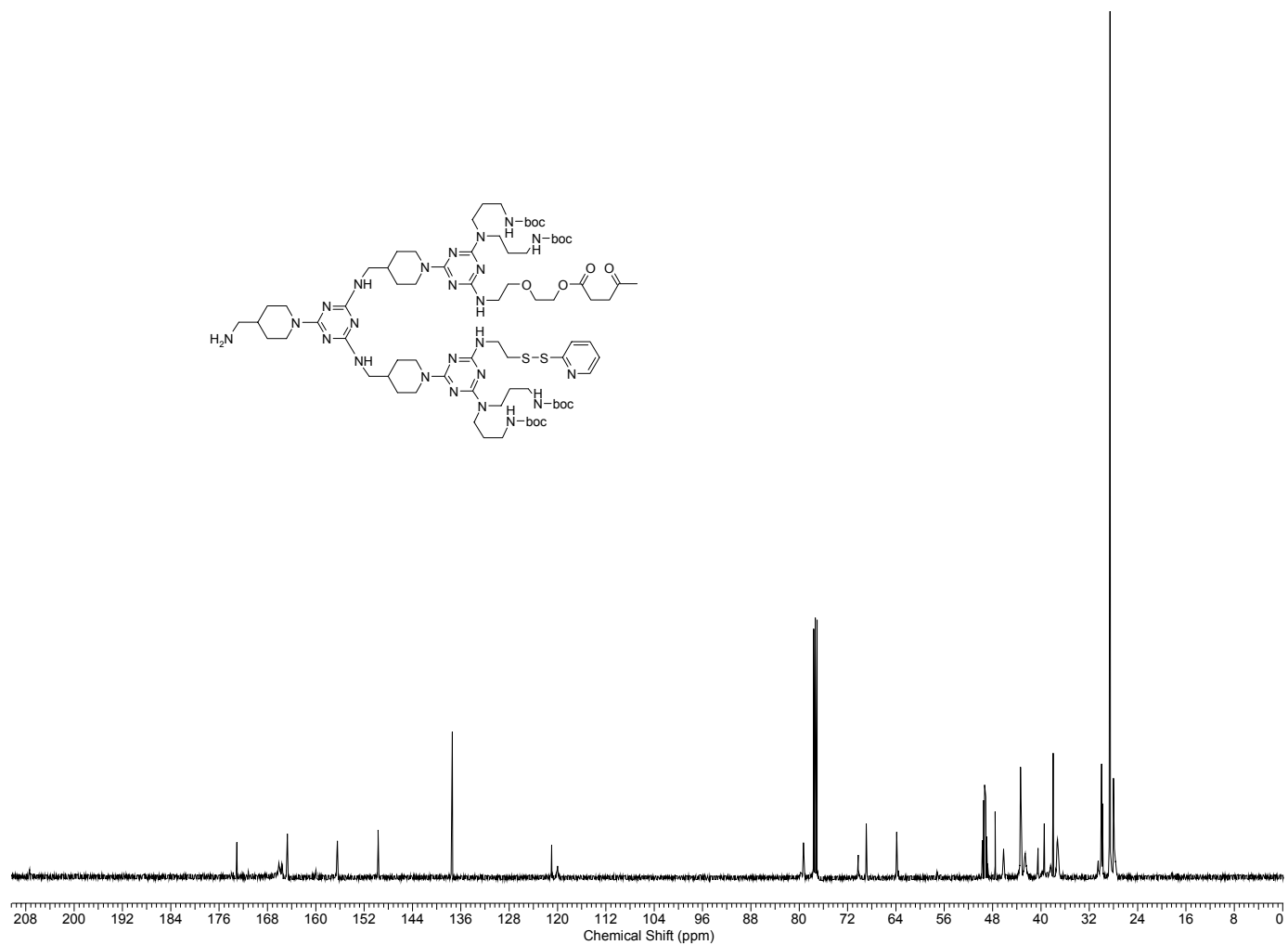




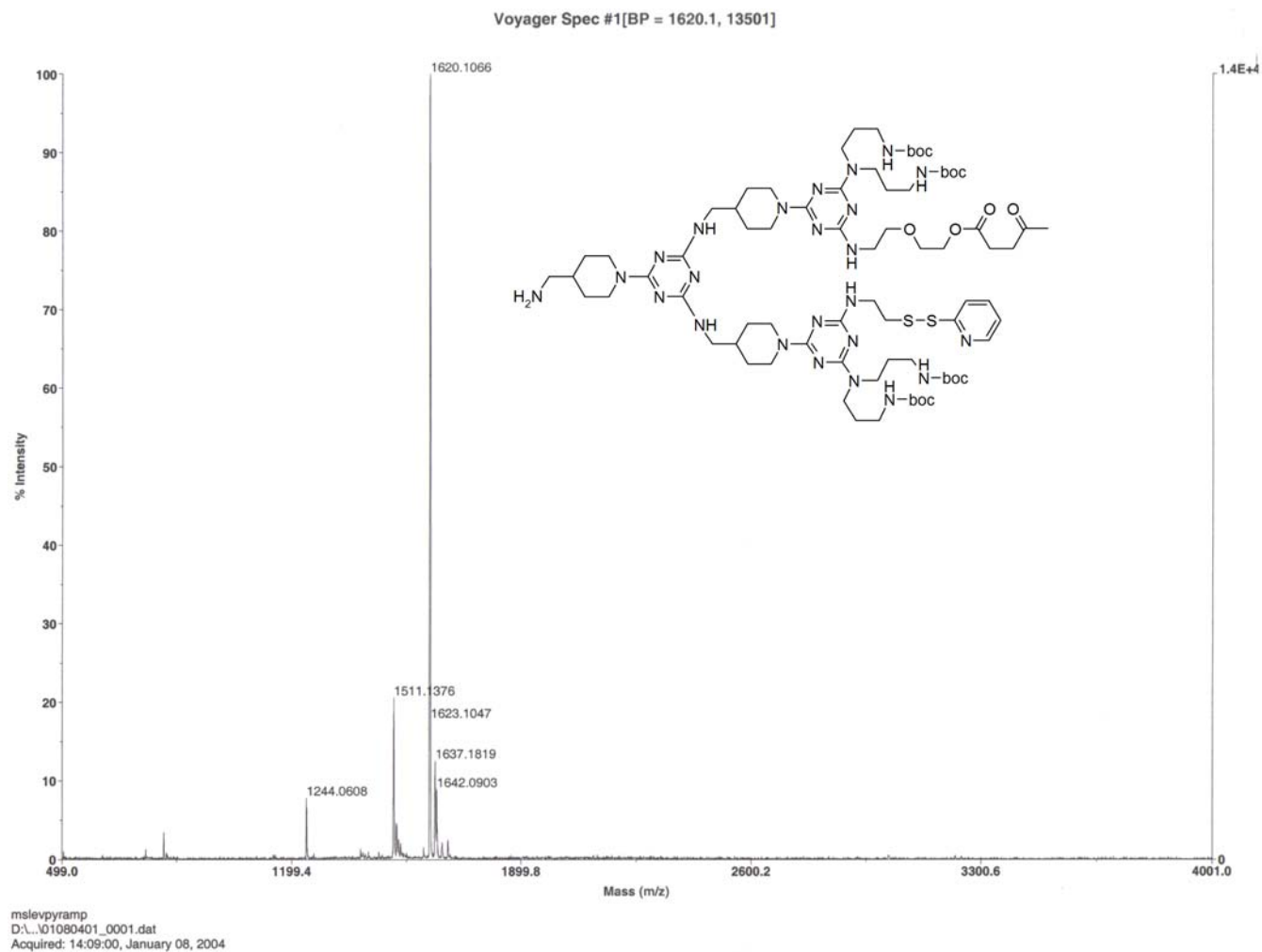
**Figure C.9c.** The ESI-TOF mass spectrum of TBDPS-Free OH-AMP, **10**.



**Figure C.10a.** The  $^1\text{H}$  NMR spectrum of Lev-Pyr-AMP, 11. (500 MHz,  $\text{CDCl}_3$ )

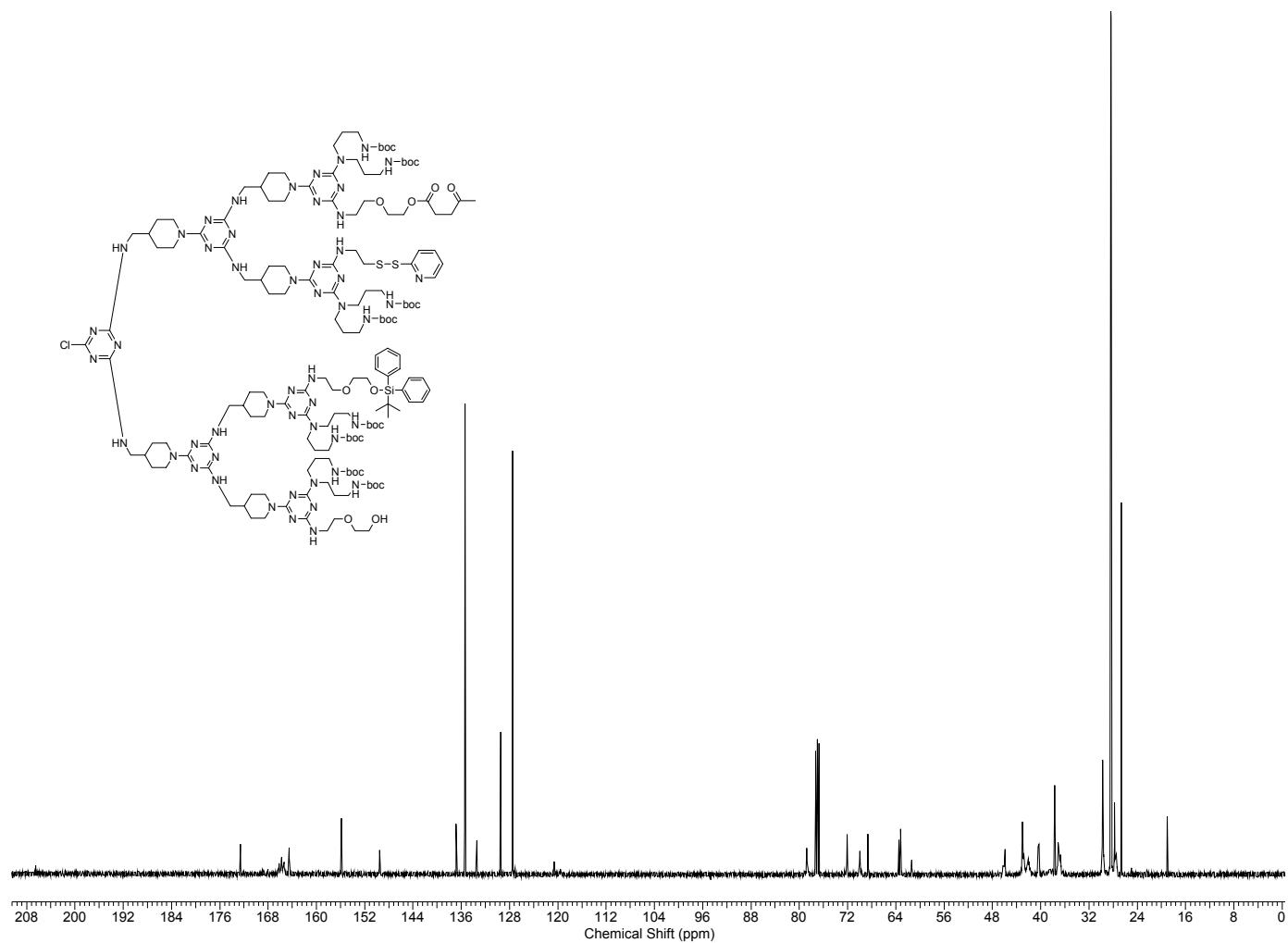


**Figure C.10b.** The  $^{13}\text{C}$  NMR spectrum of Lev-Pyr-AMP, 11. (125 MHz,  $\text{CDCl}_3$ )

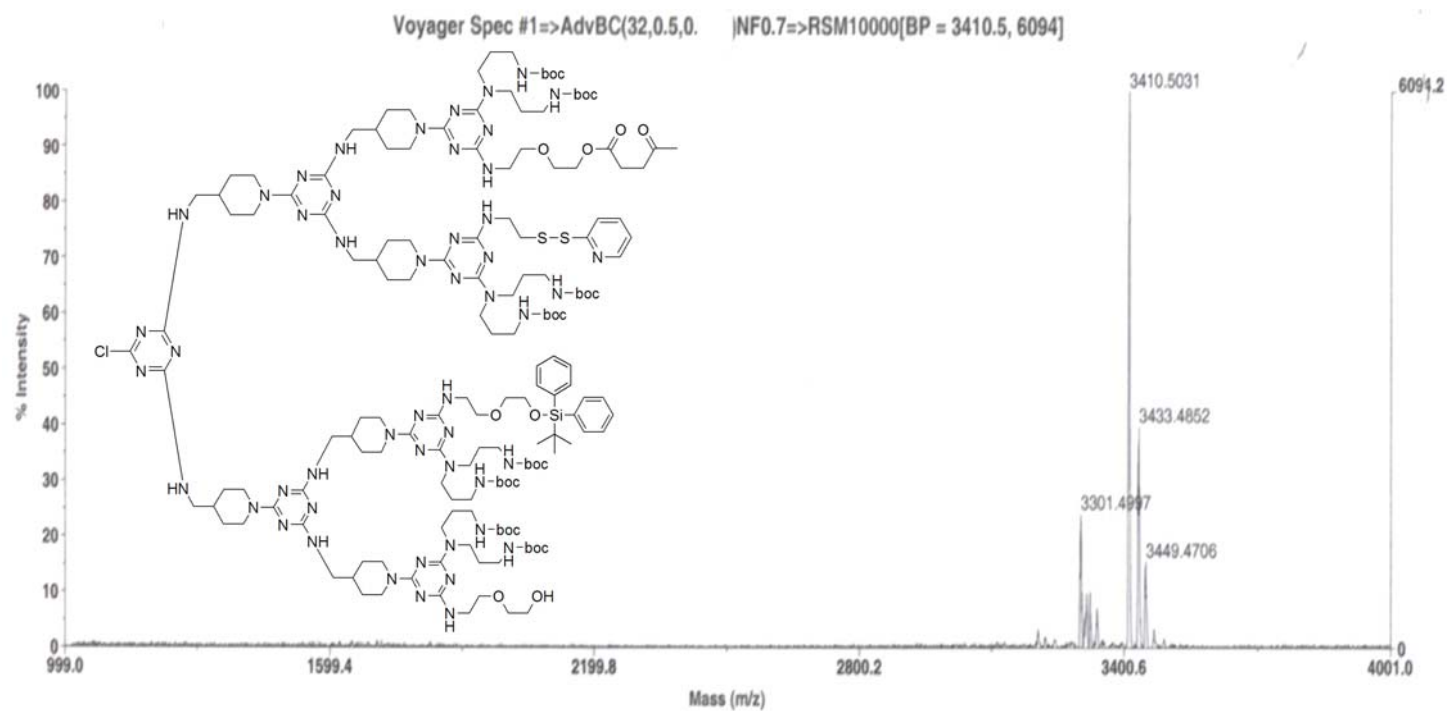


**Figure C.10c.** The MALDI-TOF mass spectrum of Lev-Pyr-AMP, **11**.



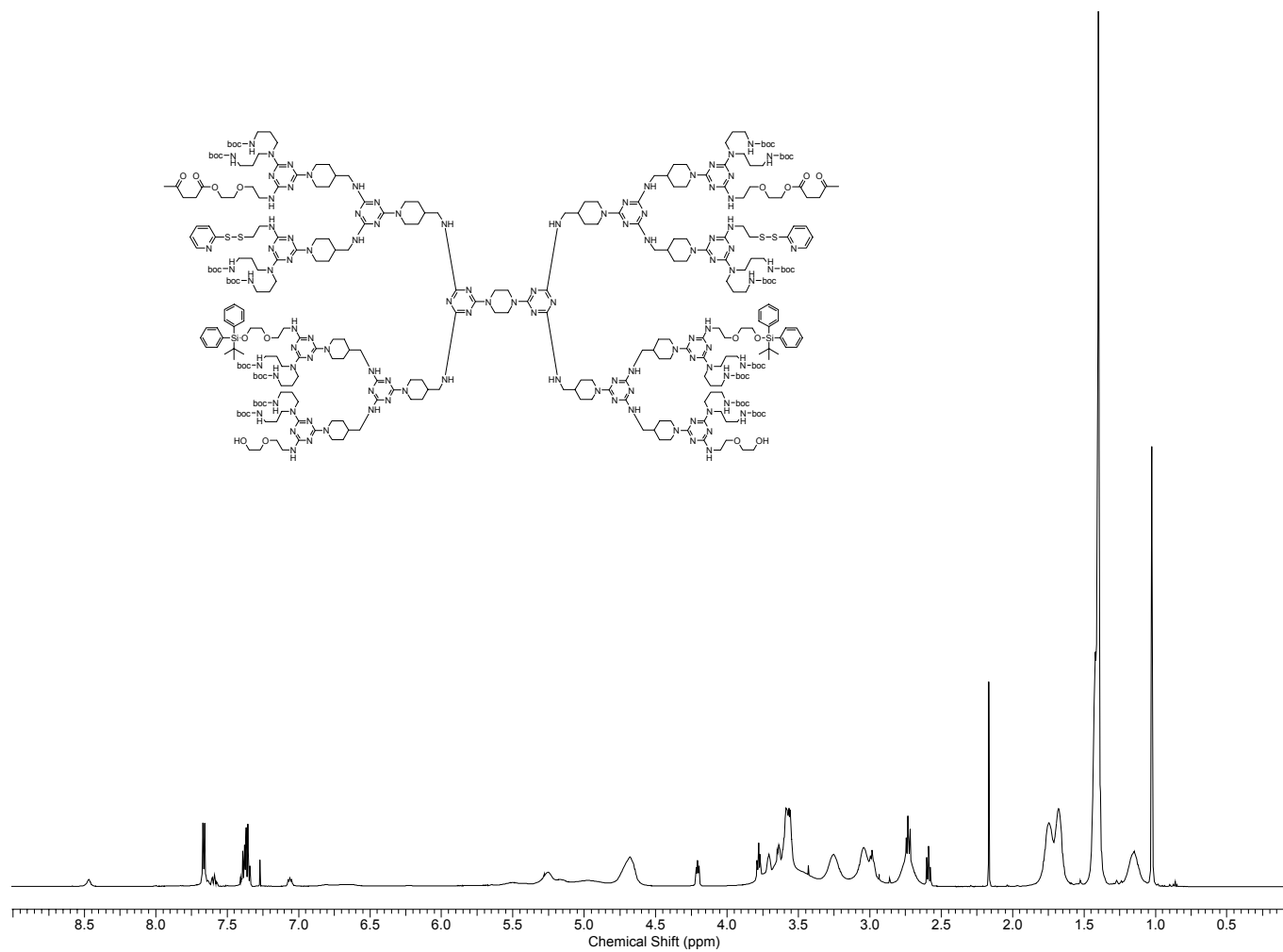


**Figure C.11b.** The  $^{13}\text{C}$  NMR spectrum of FST-Cl, 1. (500 MHz,  $\text{CDCl}_3$ )

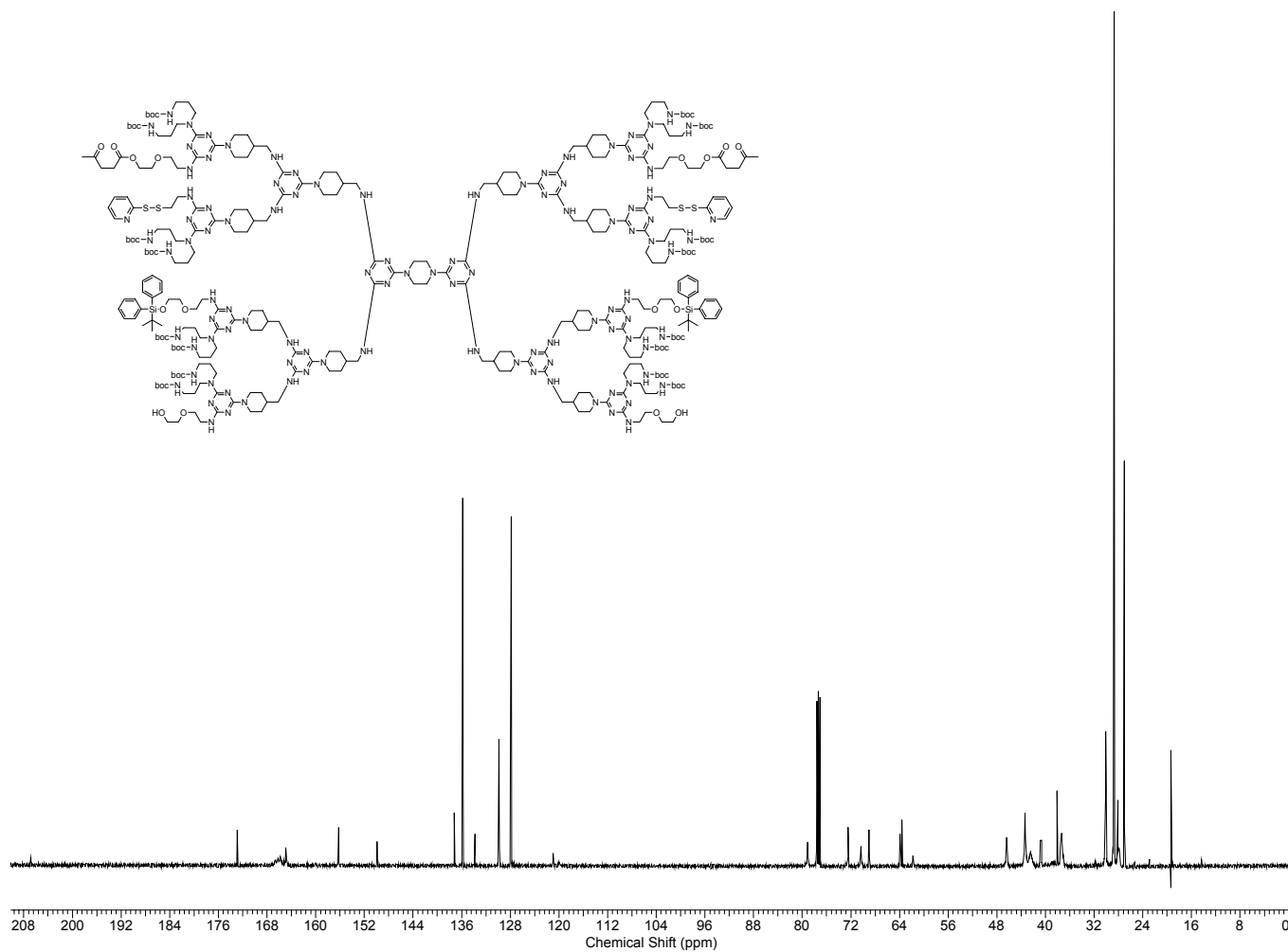


**Figure C.11c.** The MALDI-TOF mass spectrum of FST-Cl, 1.





**Figure C.12a.** The  $^1\text{H}$  NMR spectrum of FST-D, **12**. (500 MHz,  $\text{CDCl}_3$ )



**Figure C.12b.** The  $^{13}\text{C}$  NMR spectrum of FST-D, **12**. (500 MHz,  $\text{CDCl}_3$ )

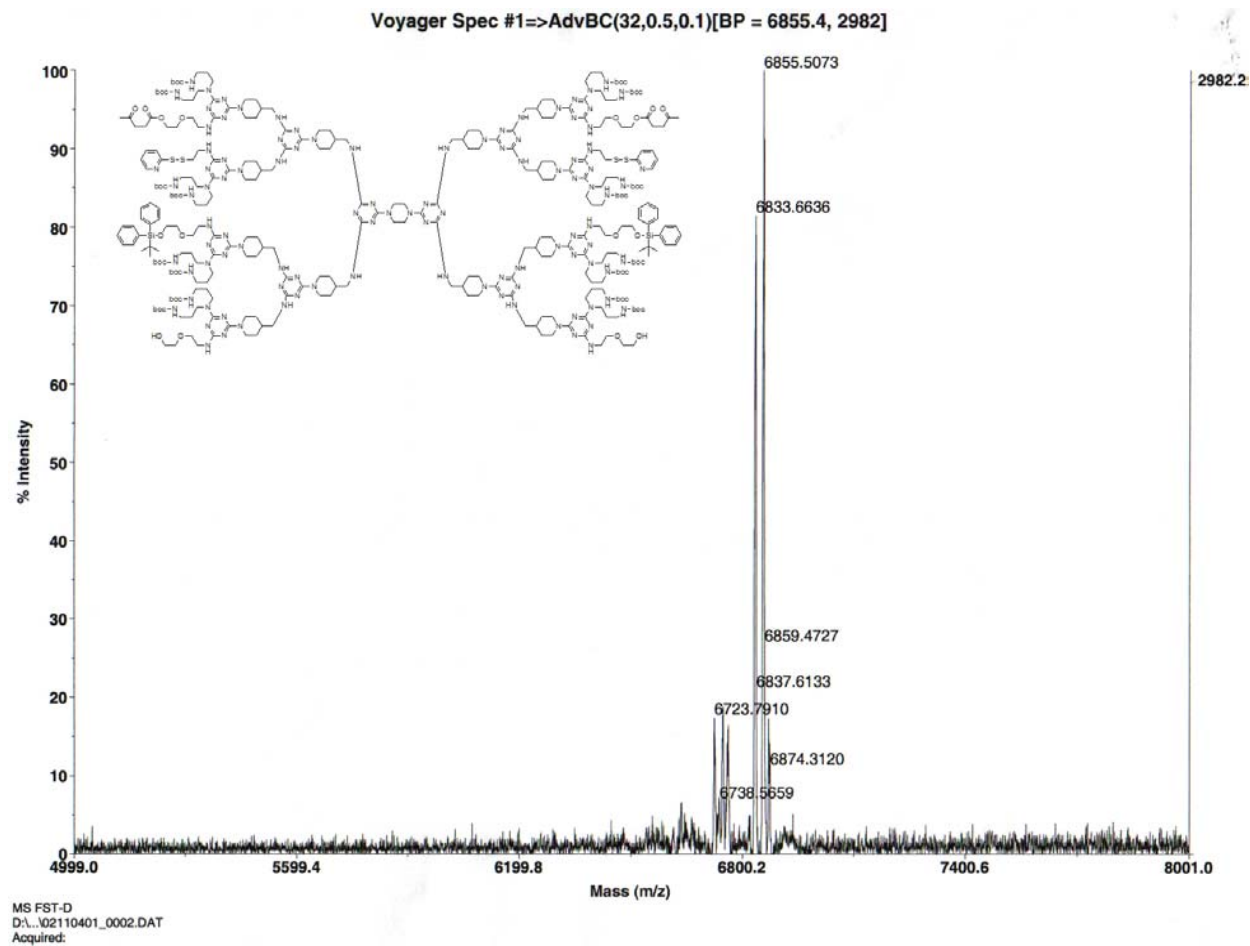
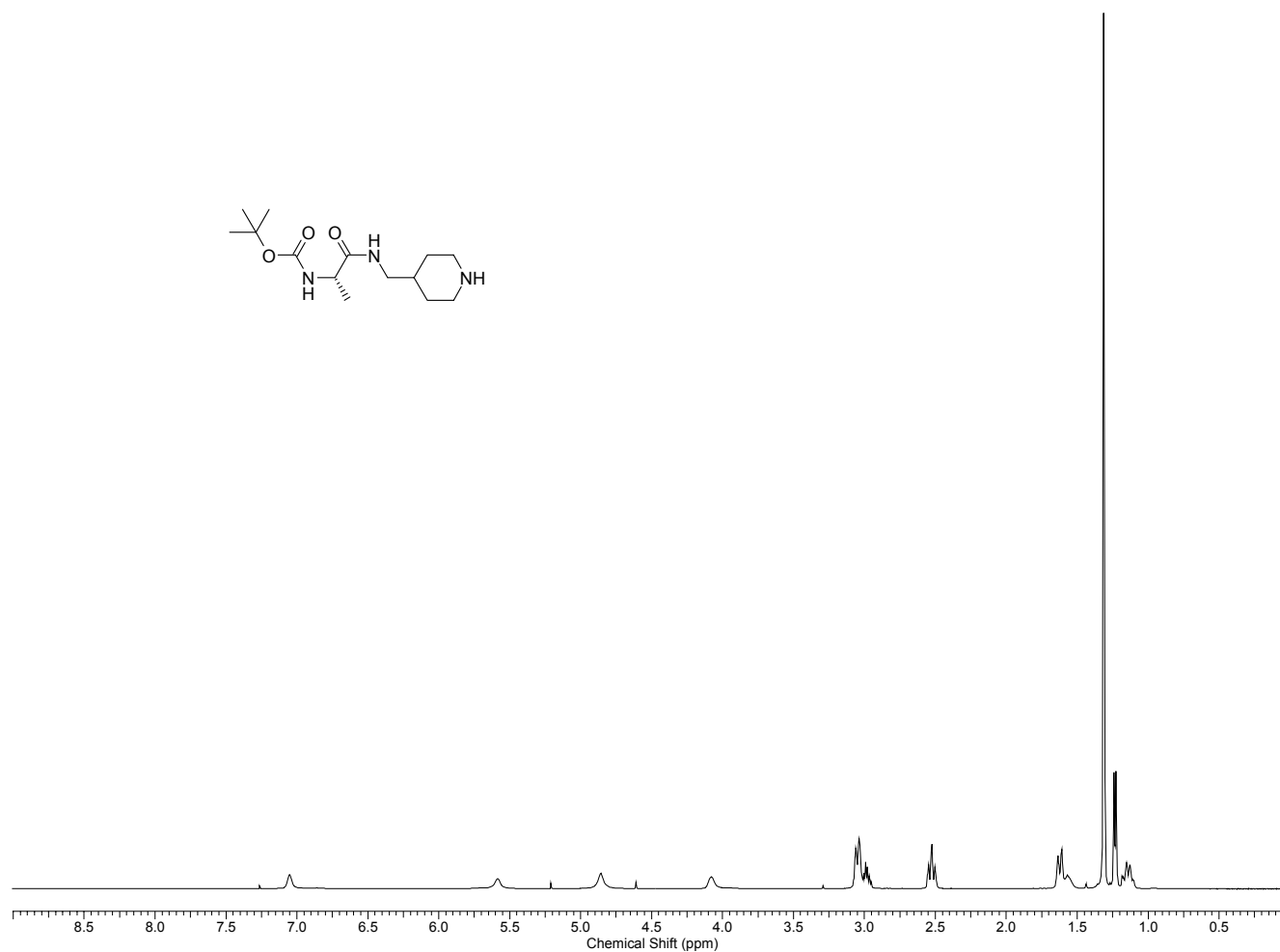
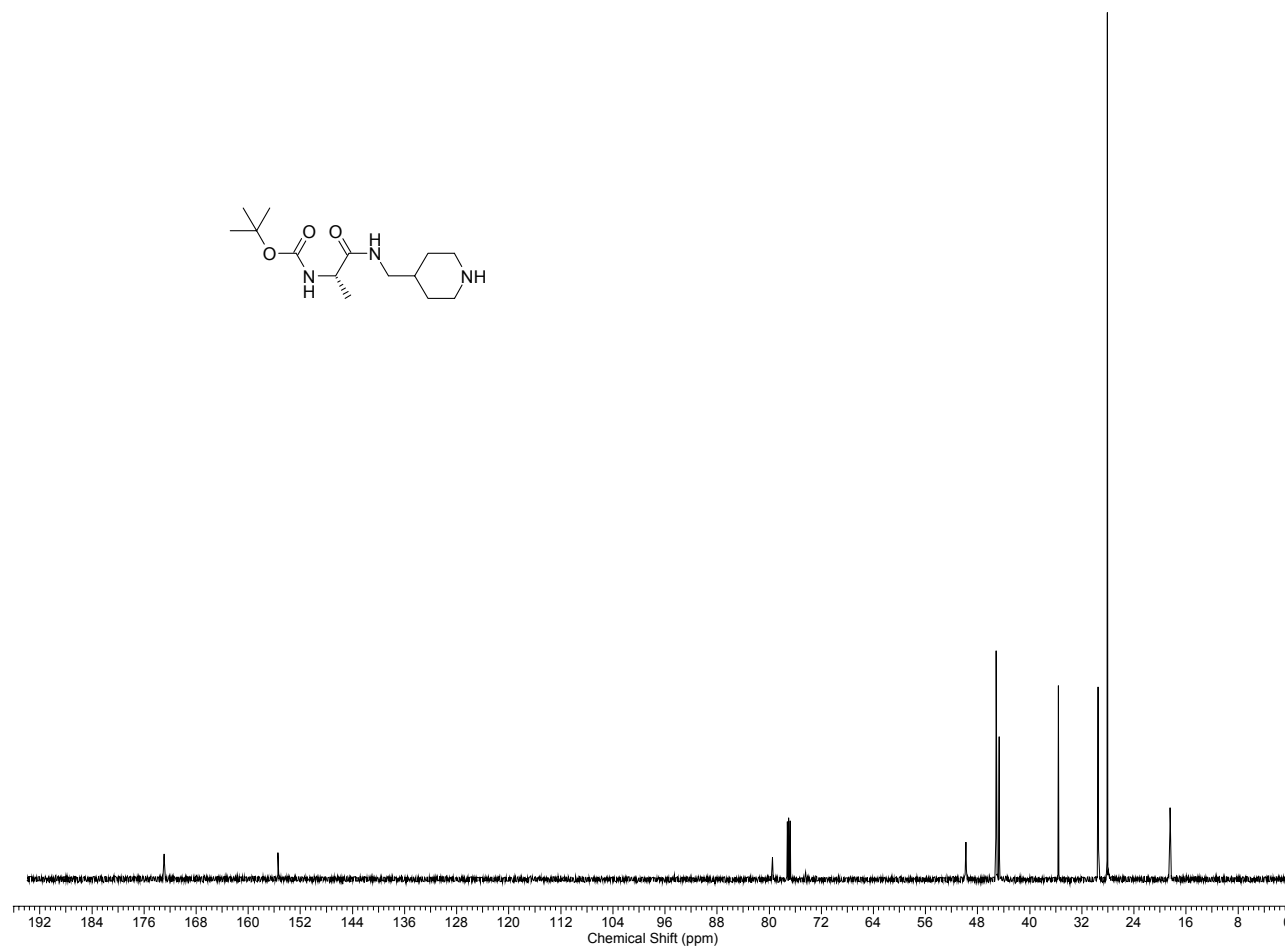


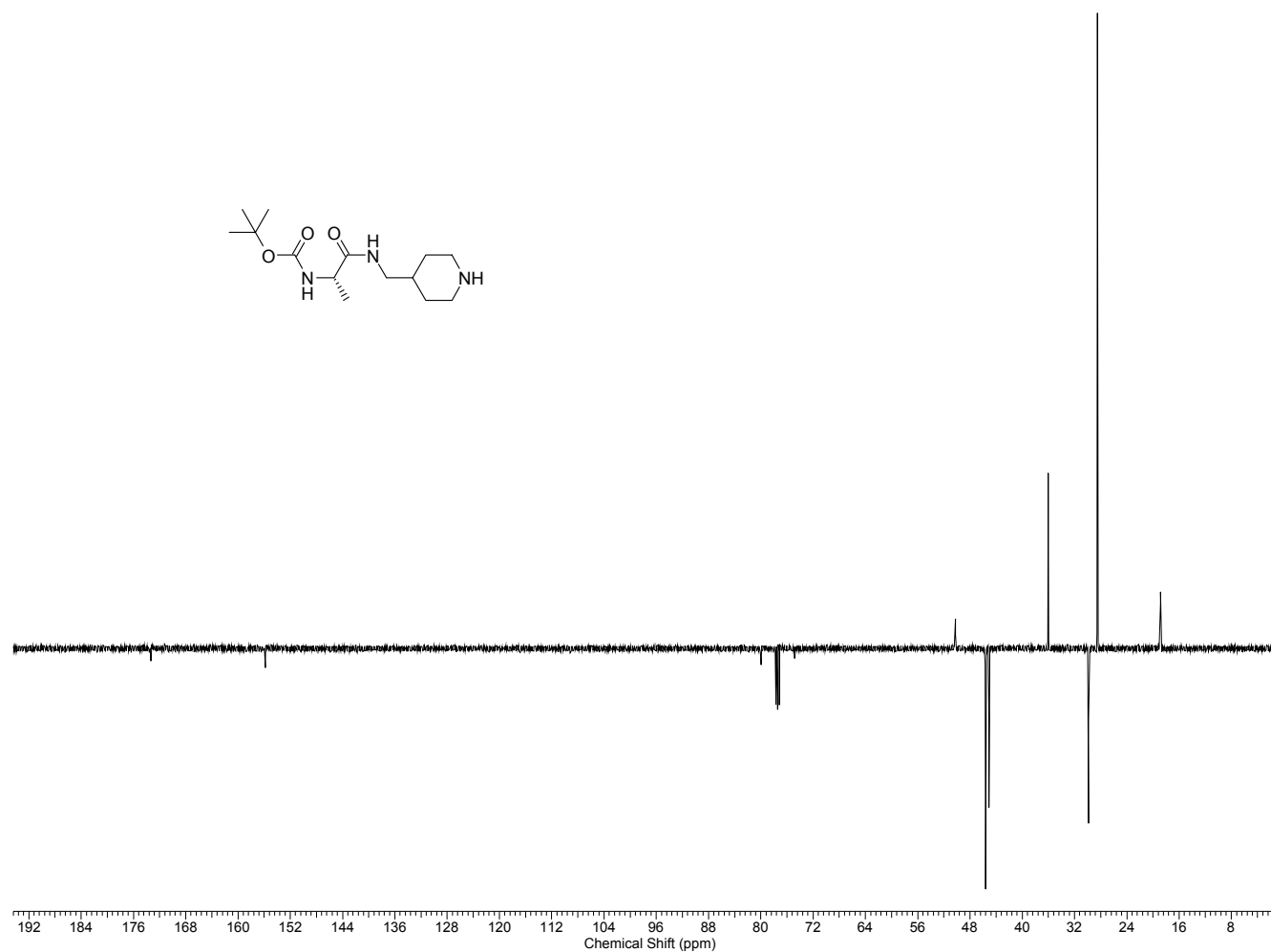
Figure C.12c. The MALDI-TOF mass spectrum of FST-D, 12.



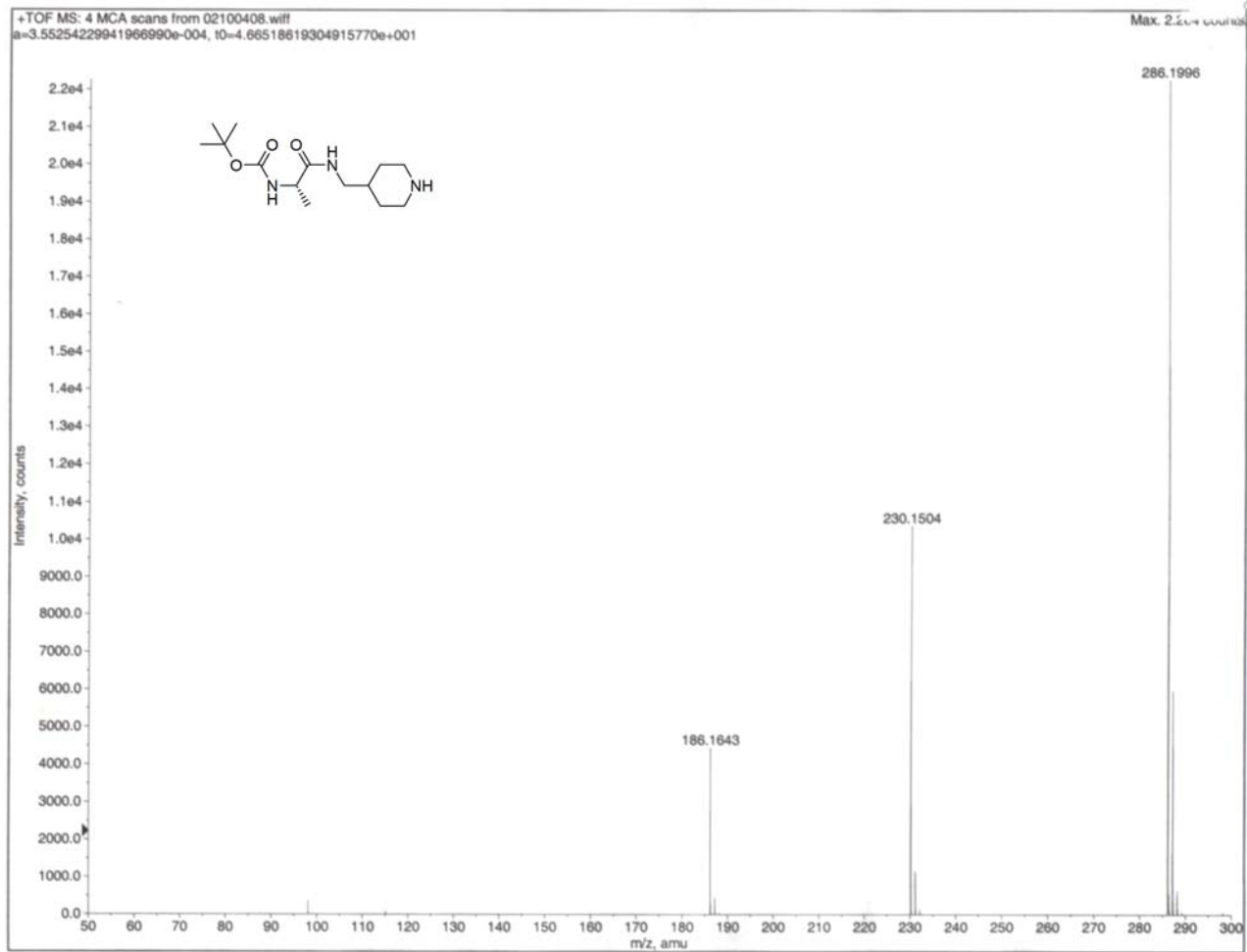
**Figure C.13a.** The <sup>1</sup>H NMR spectrum of *tert*-Butyl (S)-1-((piperidin-4-yl)methylcarbamoyl)ethylcarbamate, **13** (BOC-Ala-AMP). (500 MHz, CDCl<sub>3</sub>)



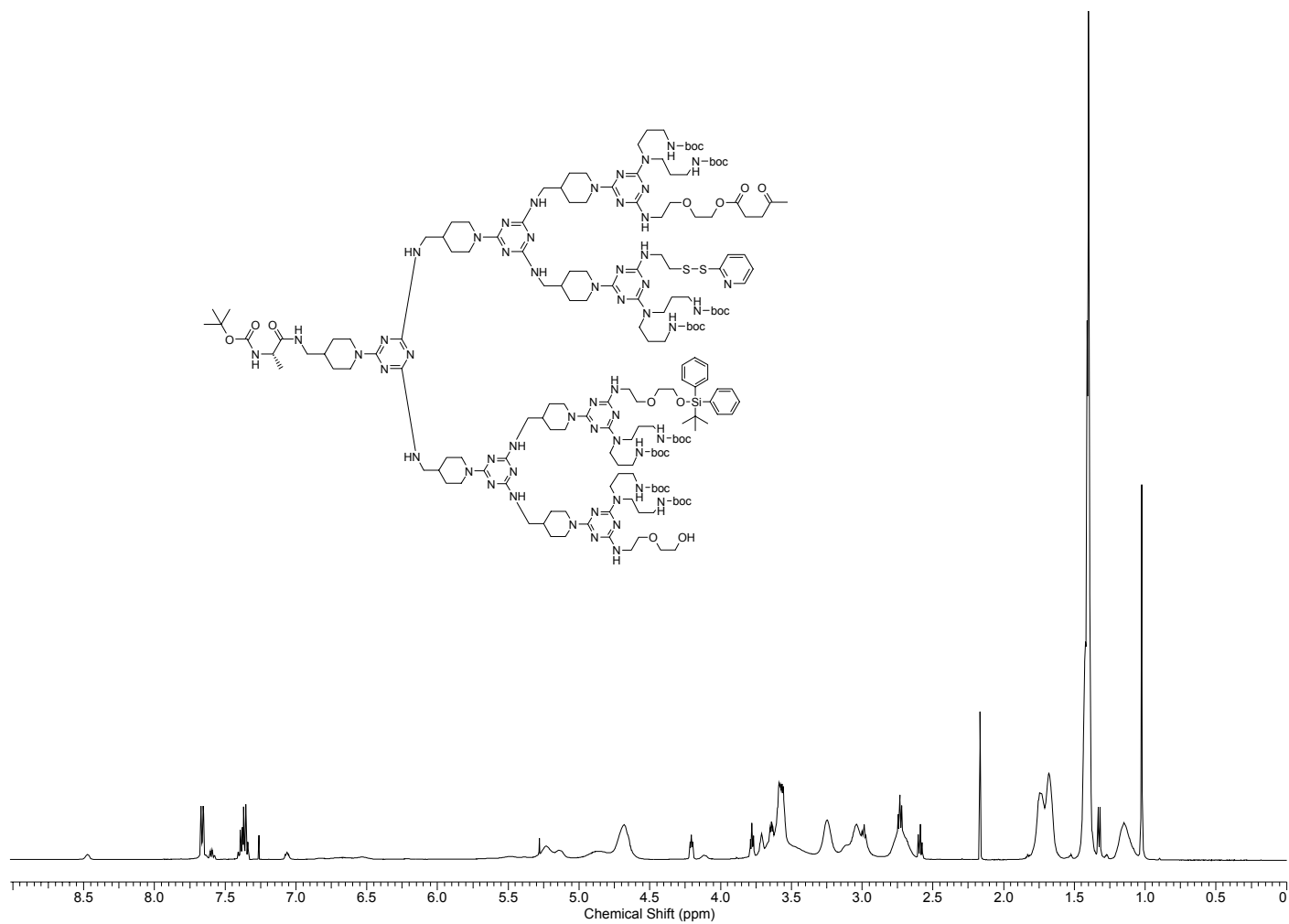
**Figure C.13b.** The <sup>13</sup>C NMR spectrum of *tert*-Butyl (S)-1-((piperidin-4-yl)methylcarbamoyl)ethylcarbamate, **13** (BOC-Ala-AMP). (500 MHz, CDCl<sub>3</sub>)



**Figure C.13c.** The <sup>13</sup>C NMR APT spectrum of *tert*-Butyl (S)-1-((piperidin-4-yl)methylcarbamoyl)ethylcarbamate, **13** (BOC-Ala-AMP). (500 MHz, CDCl<sub>3</sub>)

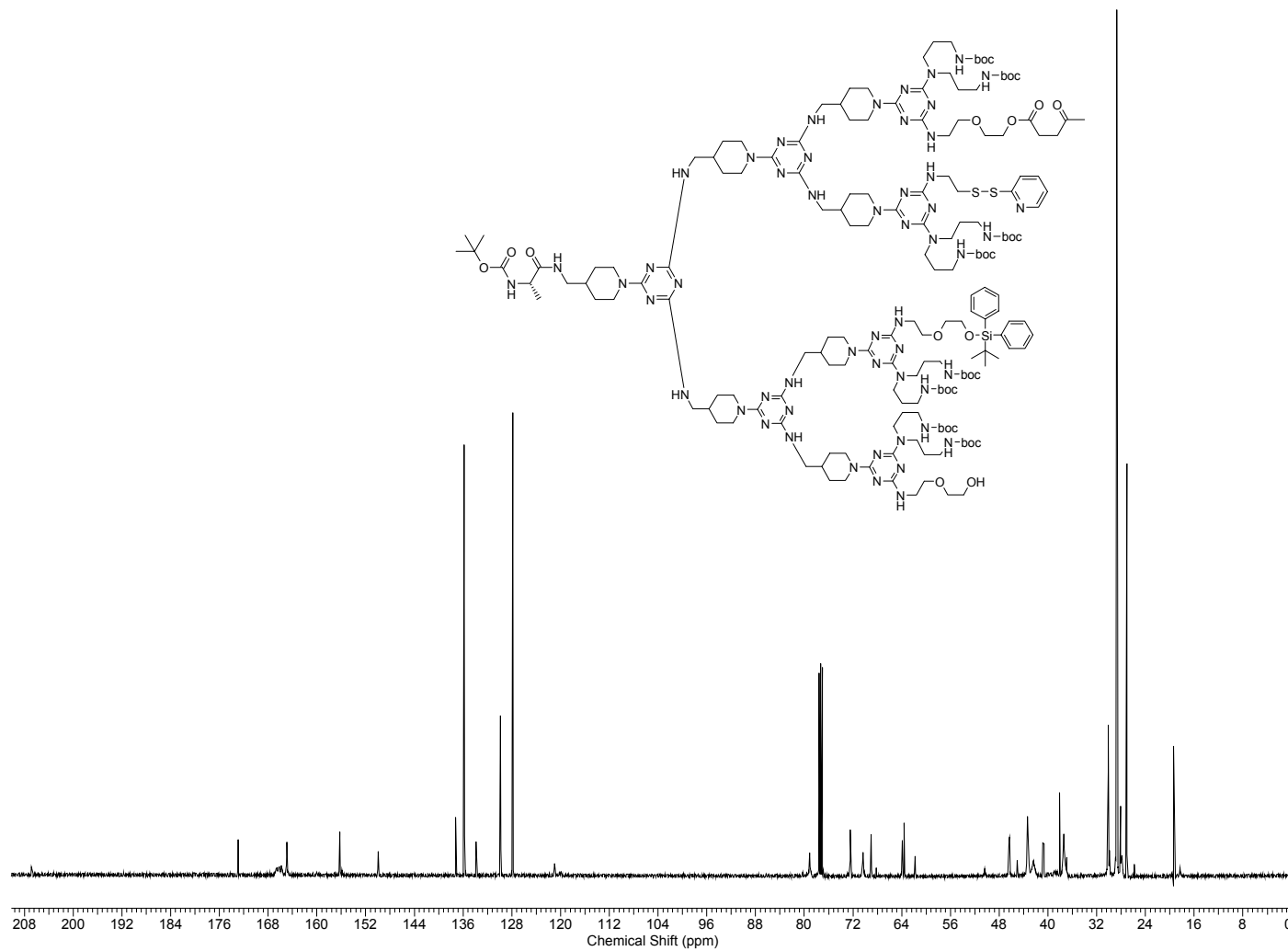


**Figure C.13d.** The ESI-TOF mass spectrum of *tert*-Butyl (S)-1-((piperidin-4-yl)methylcarbamoyl)ethylcarbamate, **13** (BOC-Ala-AMP).

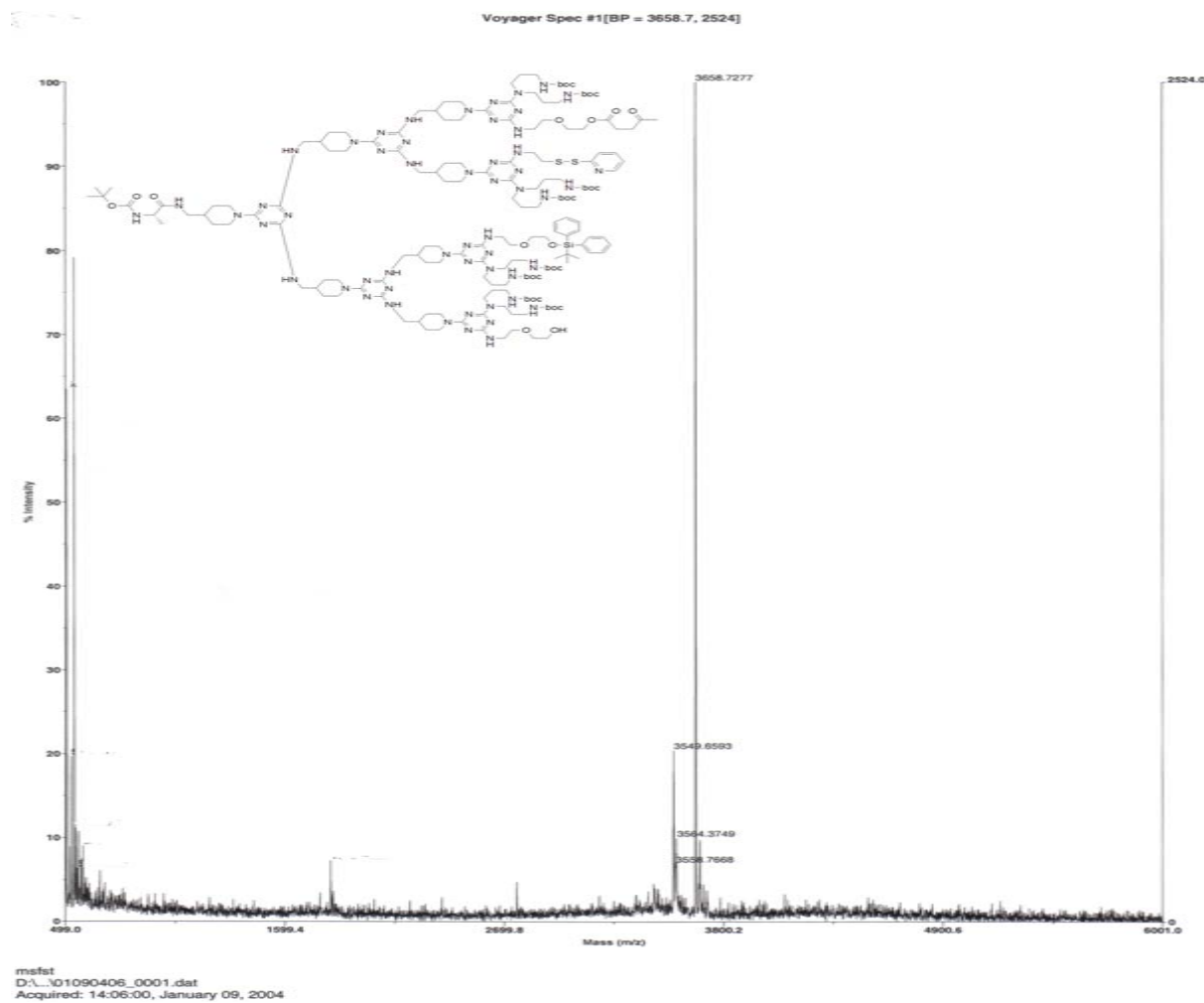


**Figure C.14a.** The  $^1\text{H}$  NMR spectrum of FST-Ala, **14**. (500 MHz,  $\text{CDCl}_3$ )

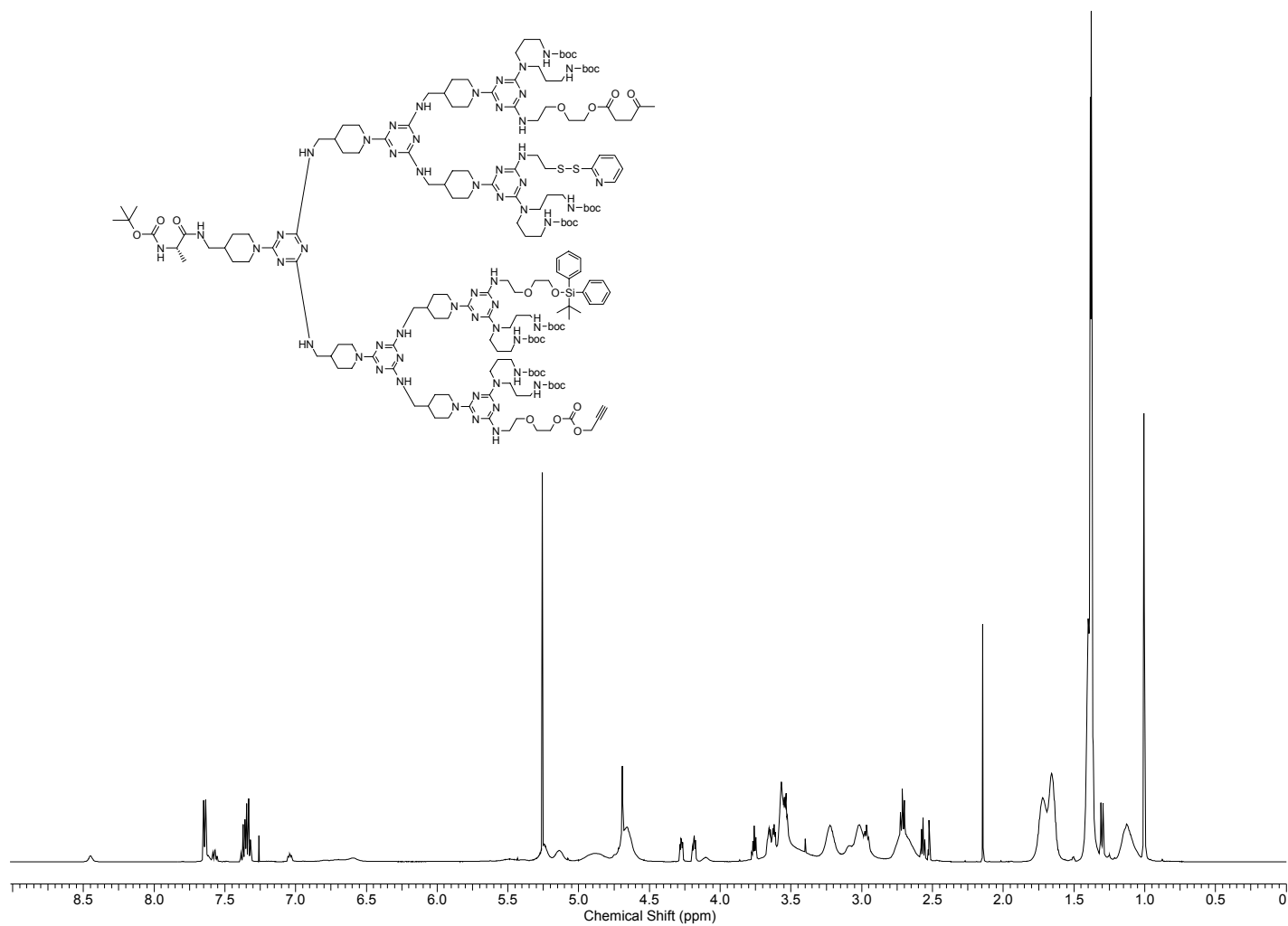




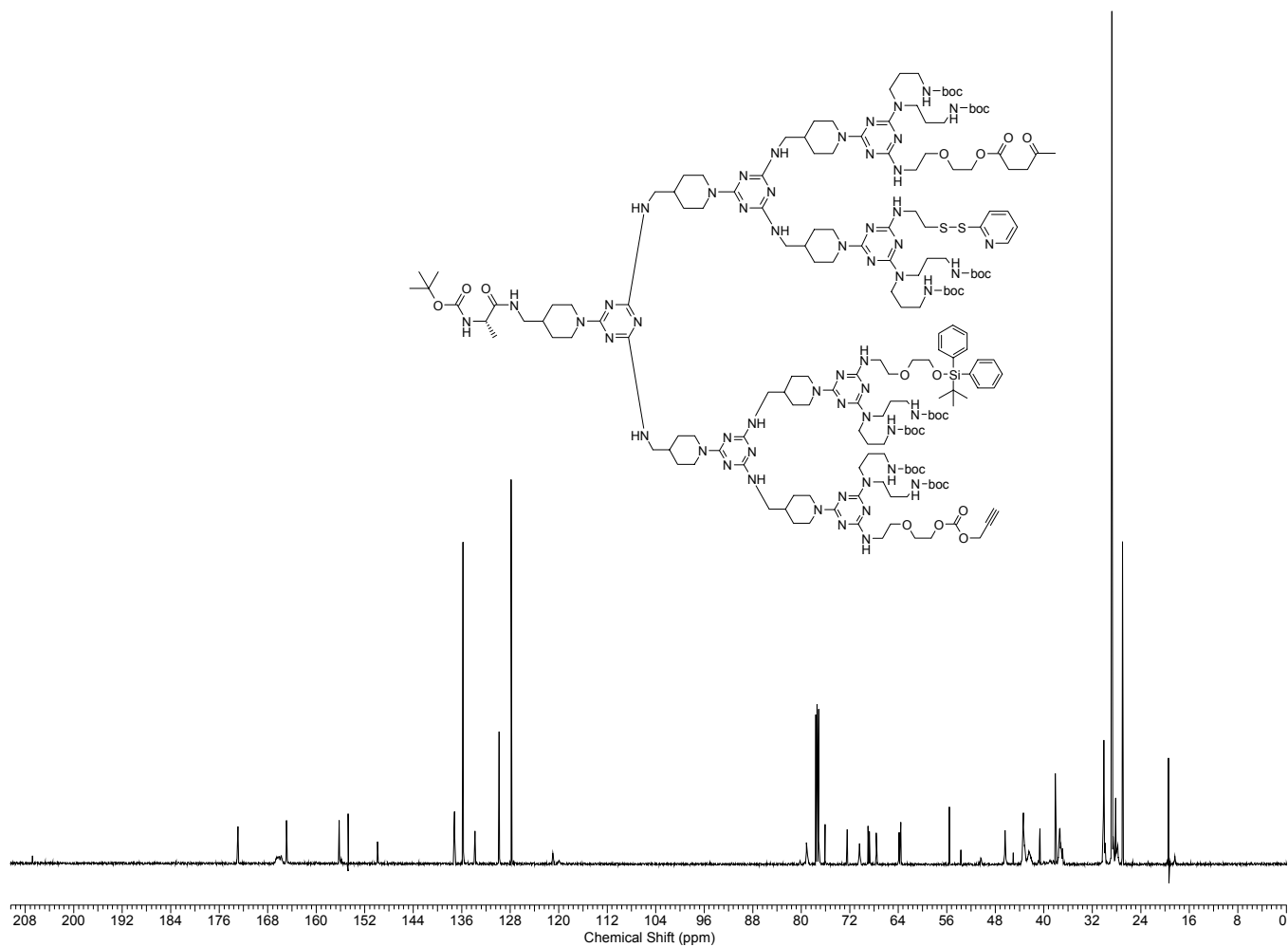
**Figure C.14b.** The  $^{13}\text{C}$  NMR spectrum of FST-Ala, 14. (125 MHz,  $\text{CDCl}_3$ )



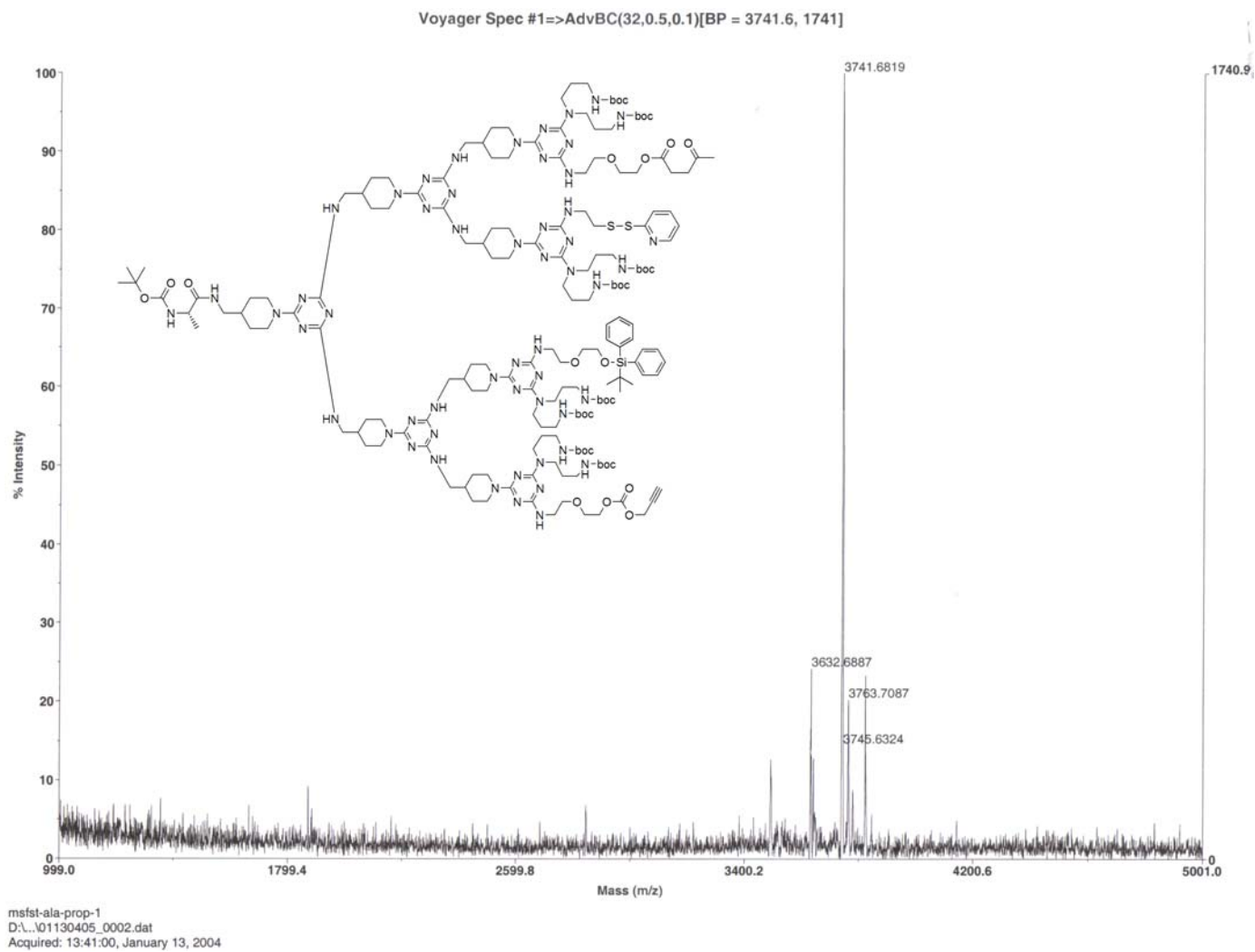
**Figure C.14c.** The MALDI-TOF mass spectrum of FST-D, 14.



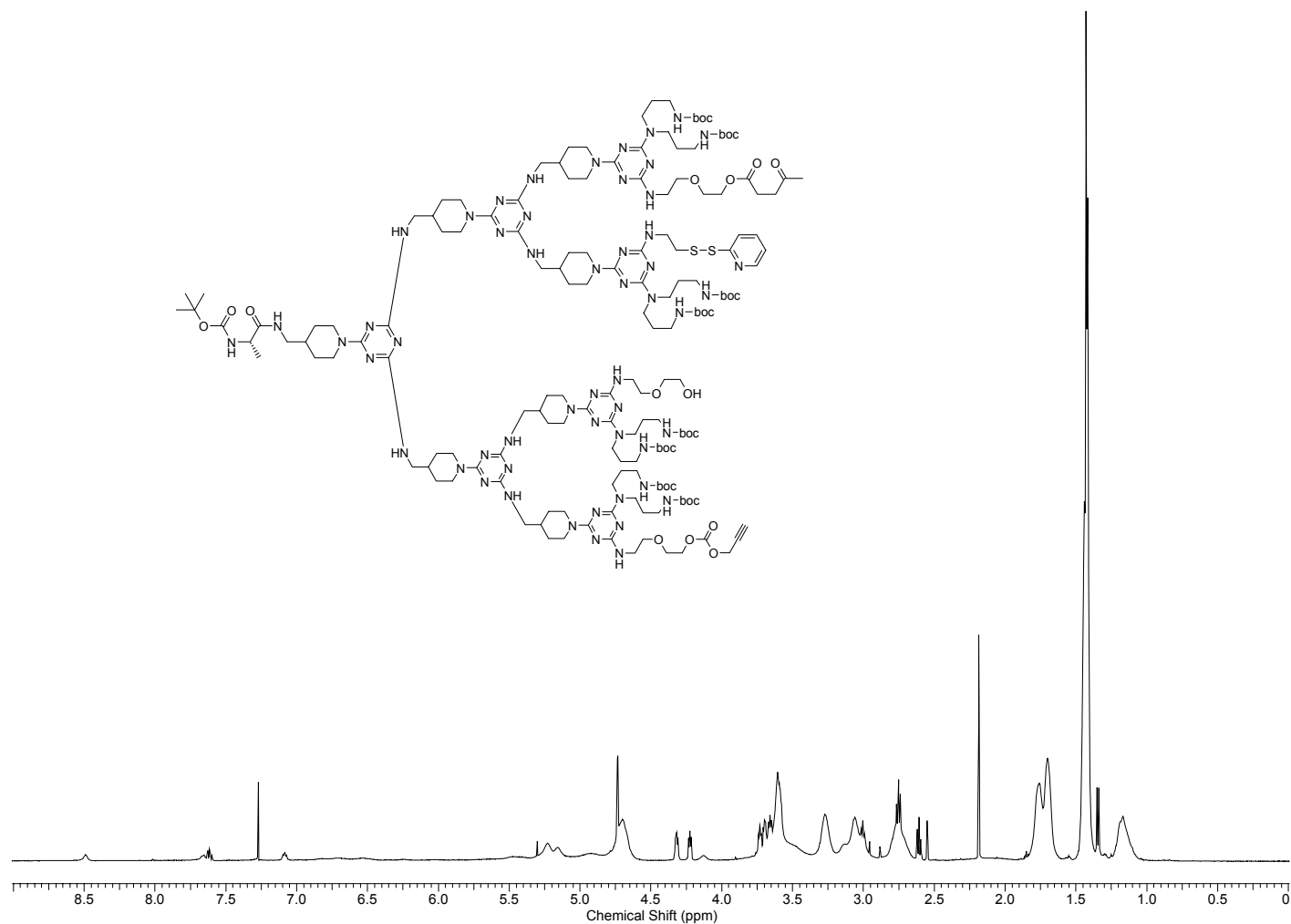
**Figure C.15a.** The <sup>1</sup>H NMR spectrum of FST-Ala-POC, **15**. (500 MHz, CDCl<sub>3</sub>)



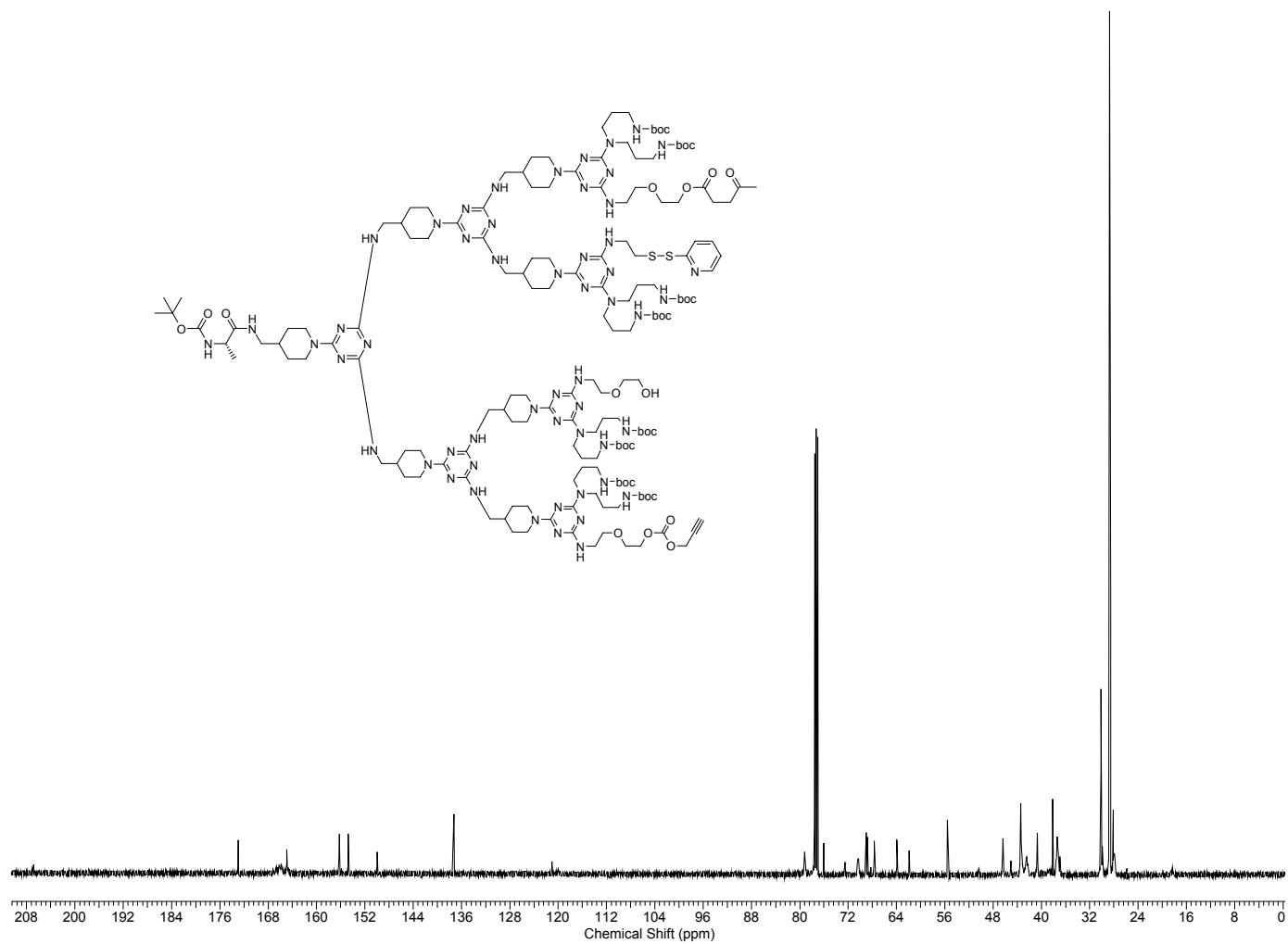
**Figure C.15b.** The  $^{13}\text{C}$  NMR spectrum of FST-Ala-POC, **15**. (125 MHz,  $\text{CDCl}_3$ )



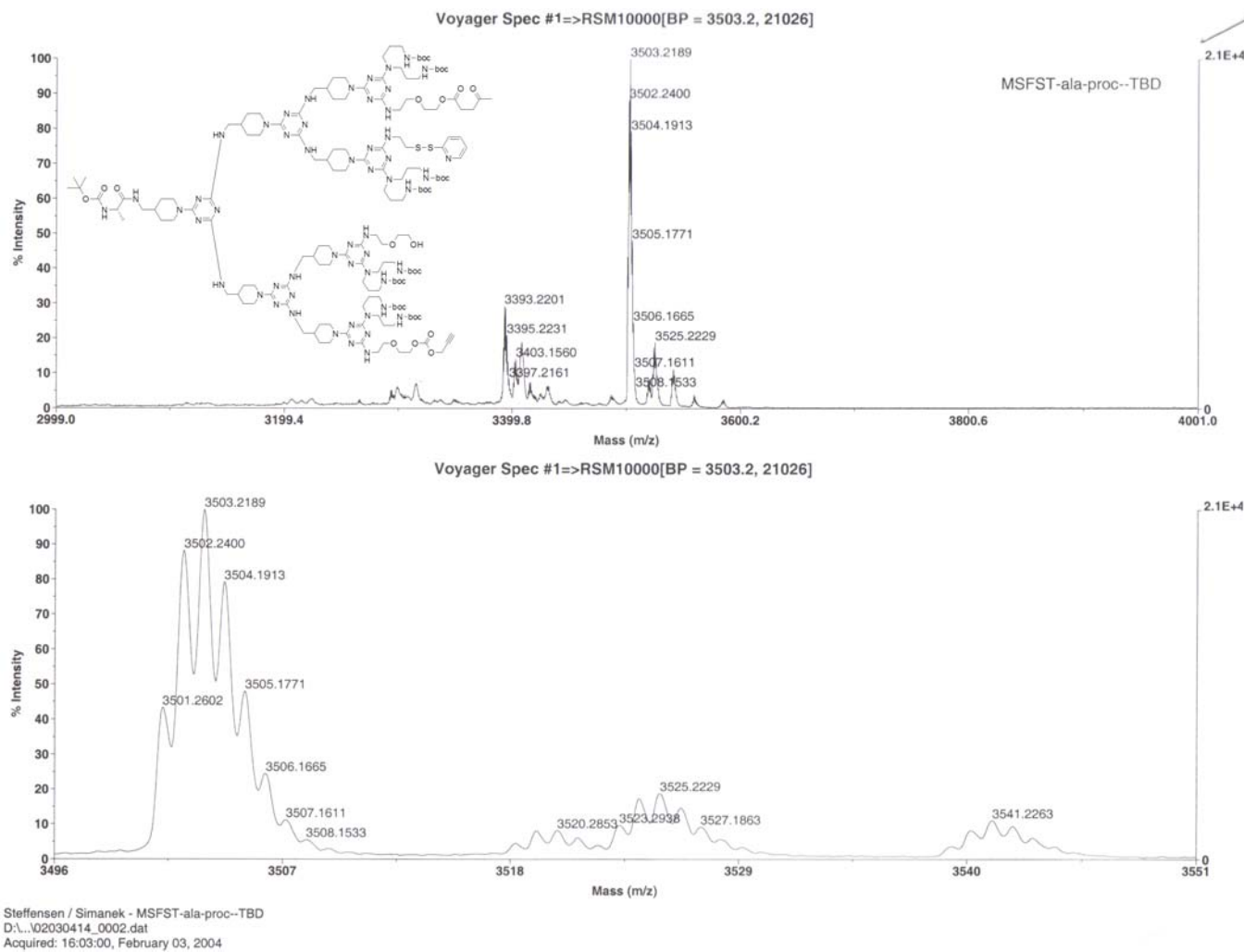
**Figure C.15c.** The MALDI-TOF mass spectrum of FST-Ala-POC, **15**.



**Figure C.16a.** The  $^1\text{H}$  NMR spectrum of FST-Ala-POC/TBDPS, **16**. (500 MHz,  $\text{CDCl}_3$ )

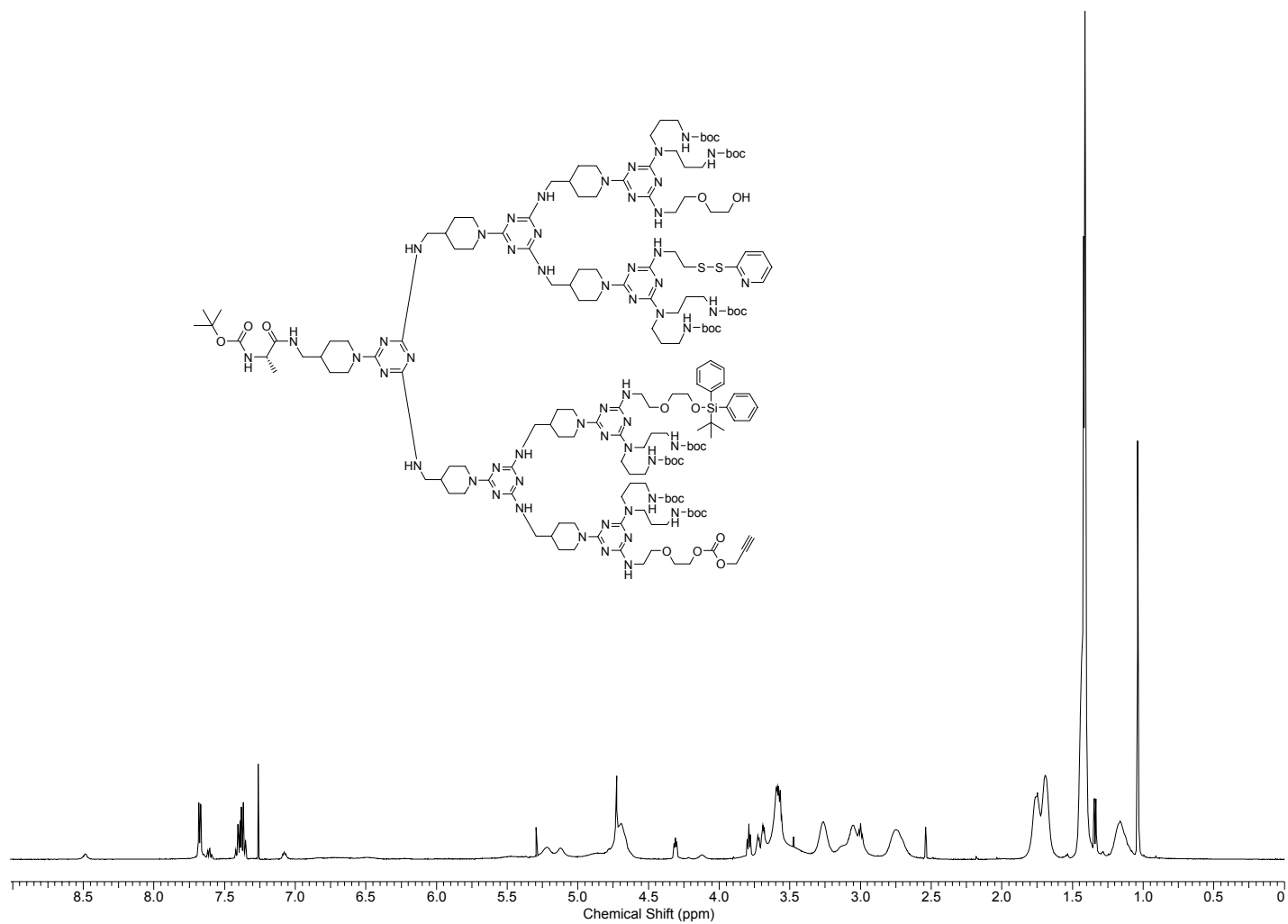


**Figure C.16b.** The  $^1\text{H}$  NMR spectrum of FST-Ala-POC/TBDPS, **16**. (125 MHz,  $\text{CDCl}_3$ )

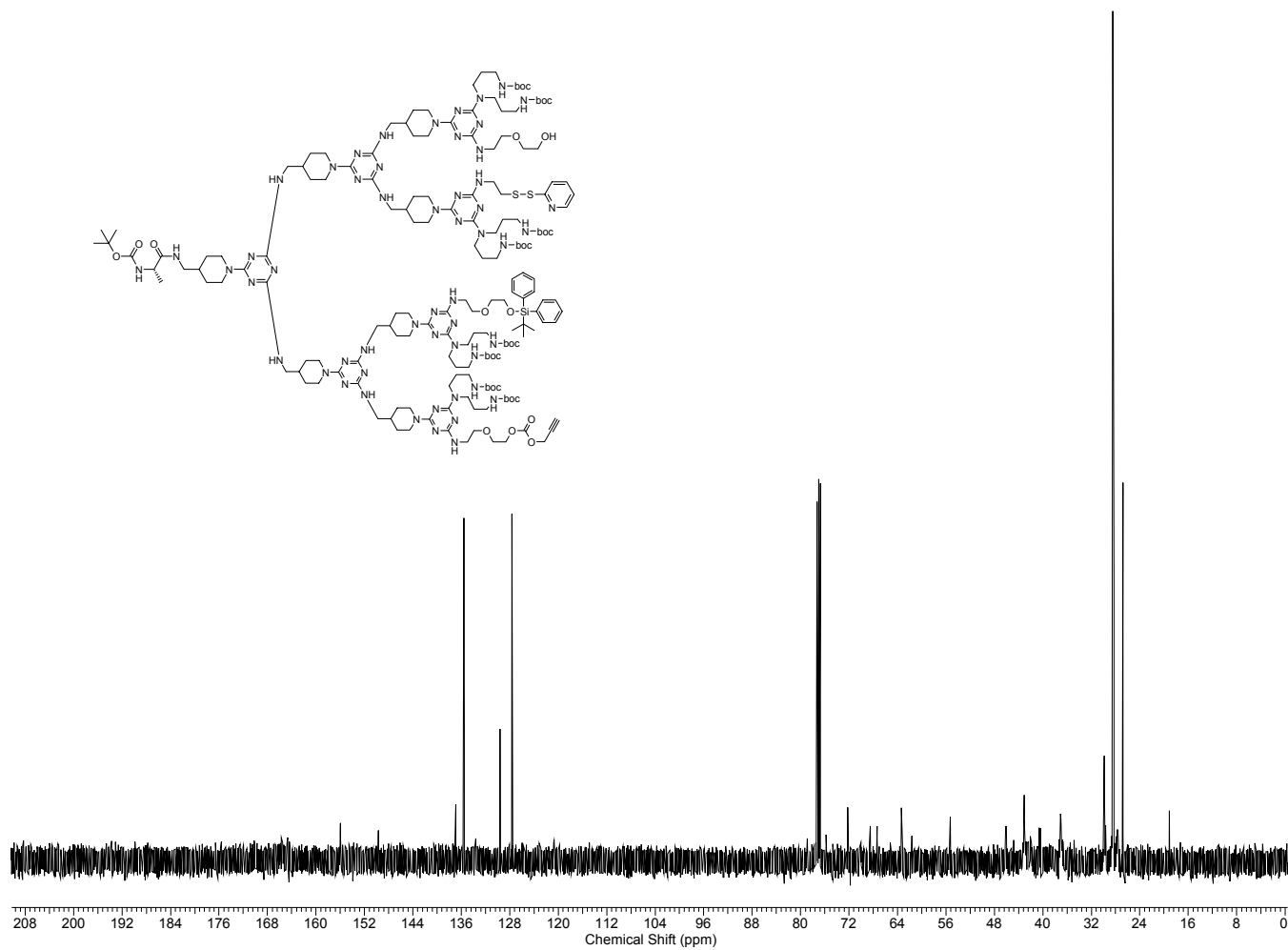


**Figure C.16c.** The MALDI-TOF mass spectrum of FST-Ala-POC/TBDPS, **16**.





**Figure C.17a.** The  $^1\text{H}$  NMR spectrum of FST-Ala-POC/Lev, **17**. (500 MHz,  $\text{CDCl}_3$ )



**Figure C.17b.** The  $^{13}\text{C}$  NMR spectrum of FST-Ala-POC/Lev, **17**. (125 MHz,  $\text{CDCl}_3$ )

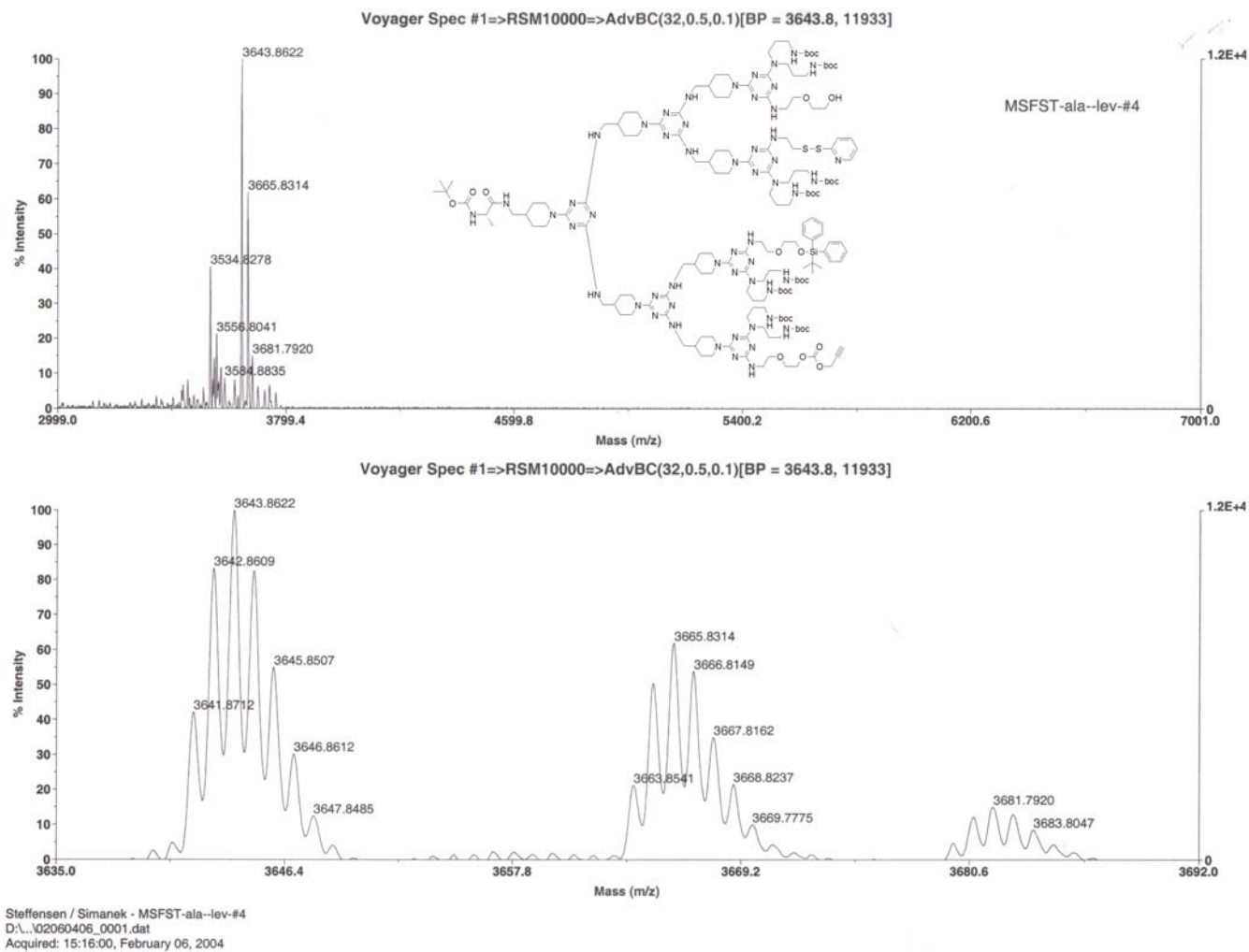
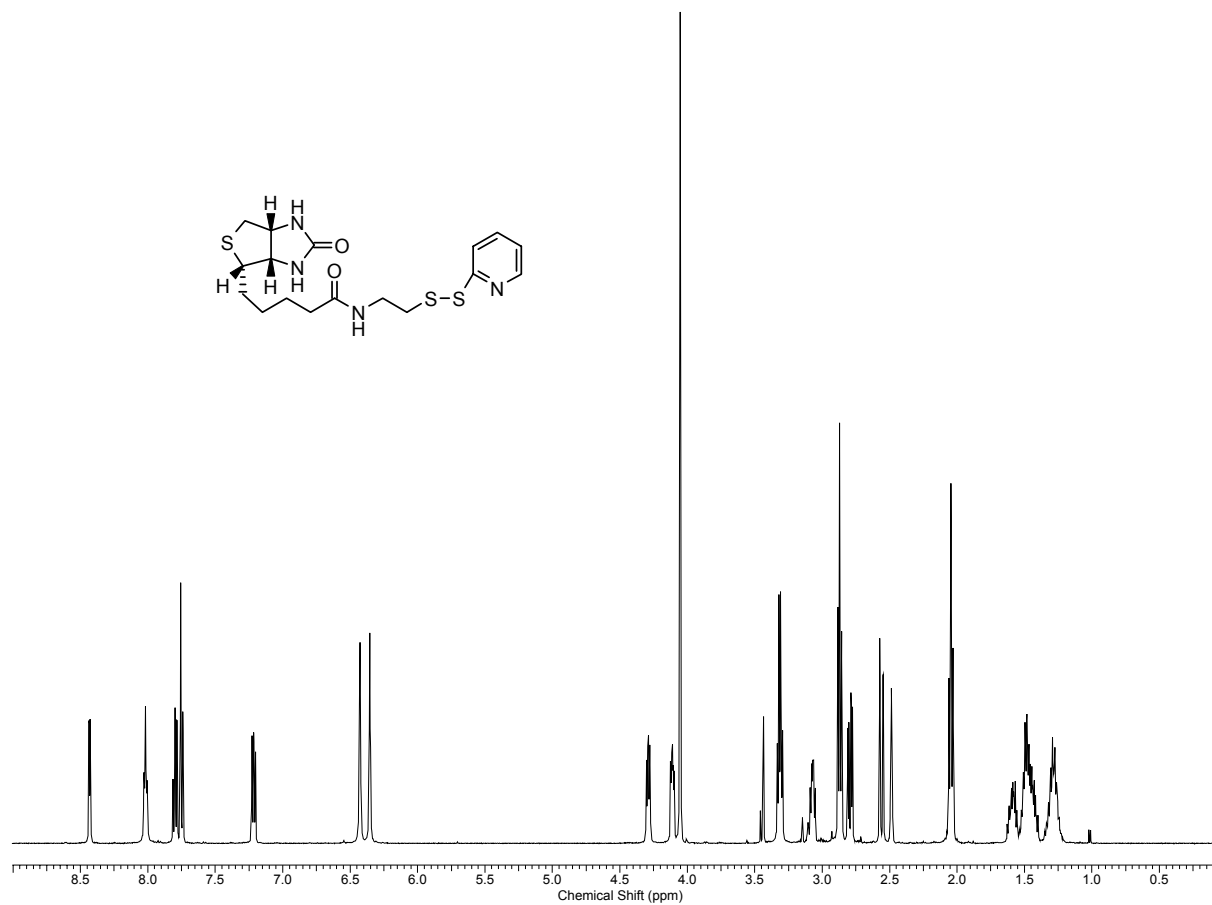
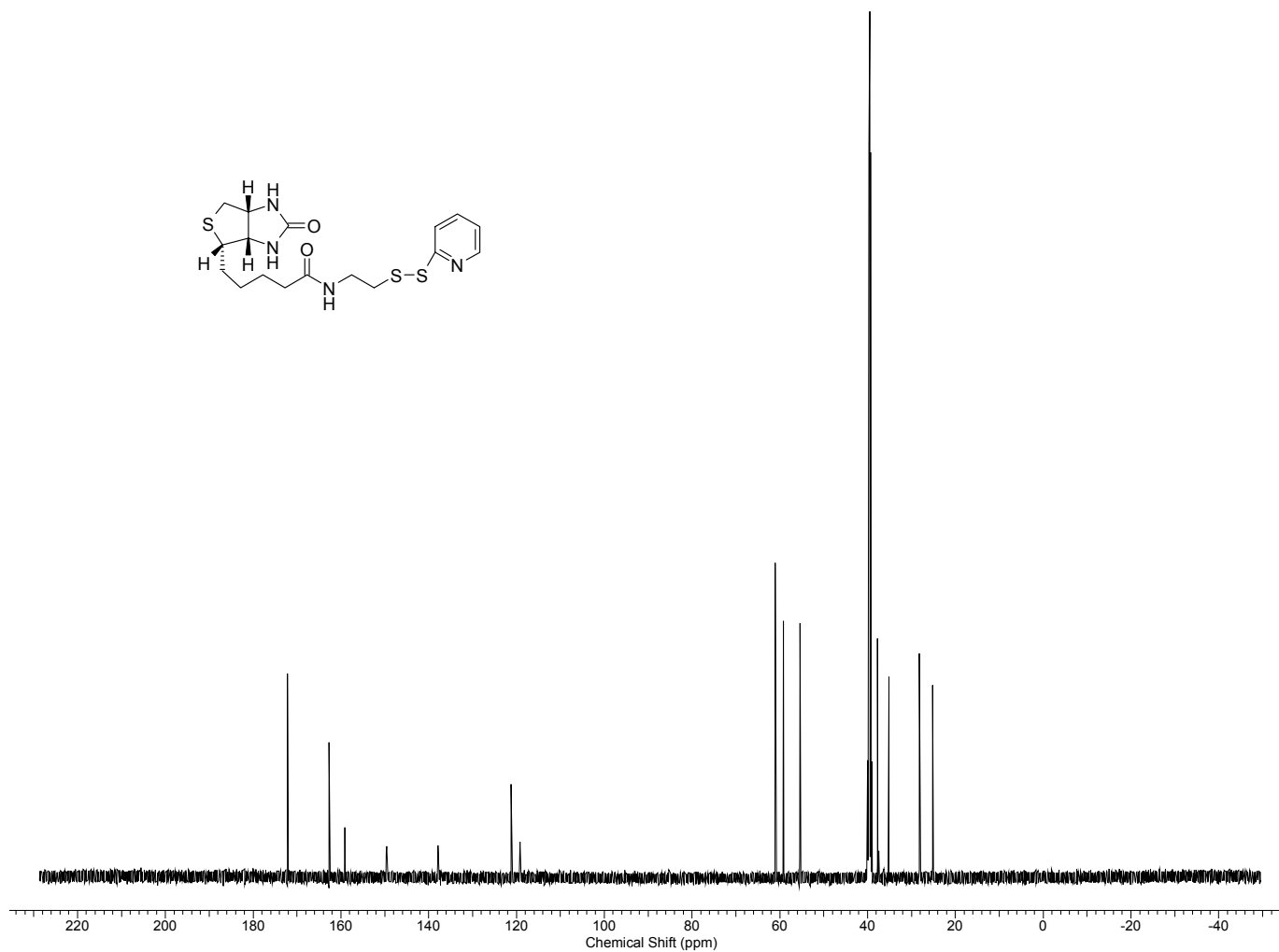


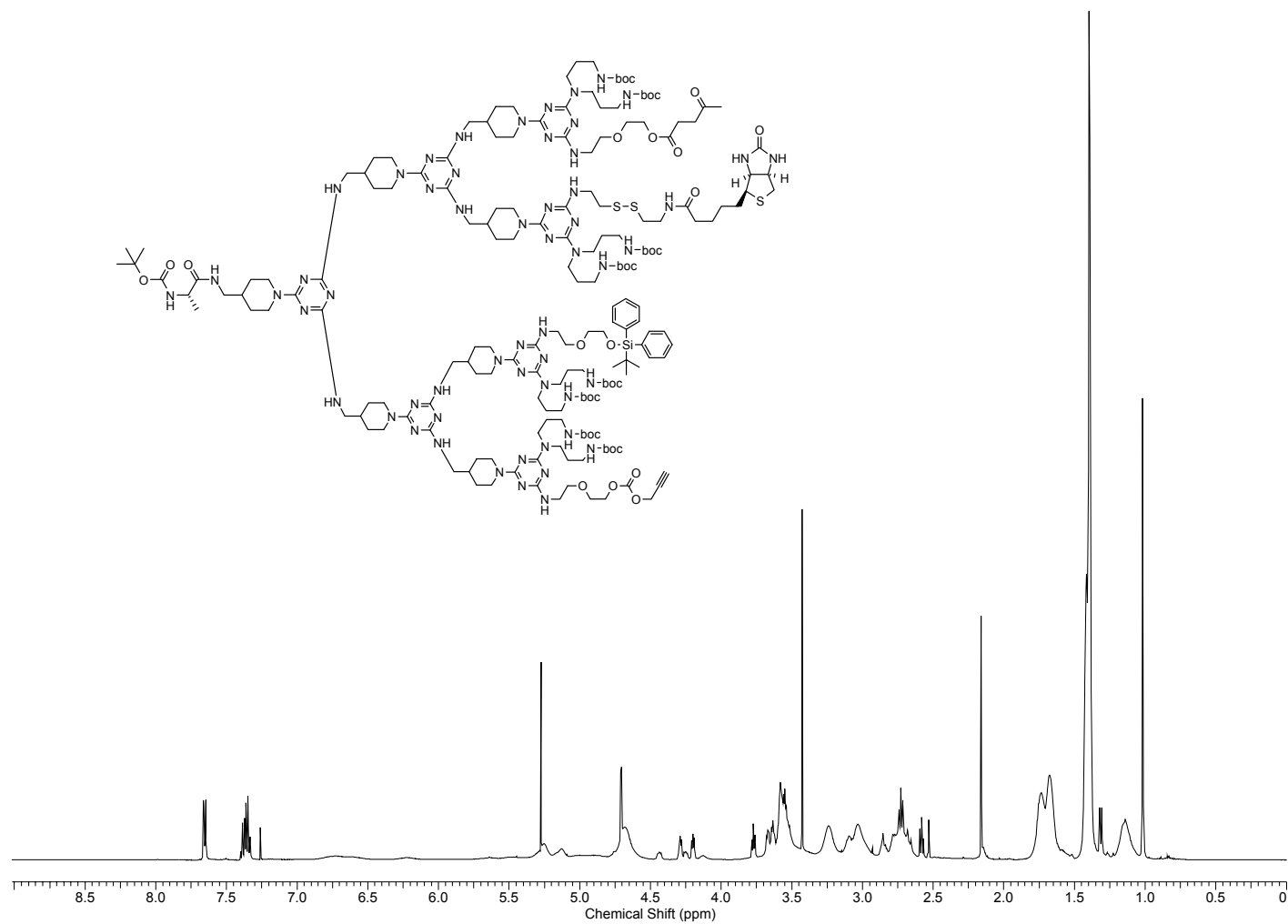
Figure C.17c. The MALDI-TOF mass spectrum of FST-Ala-POC/Lev, 17.



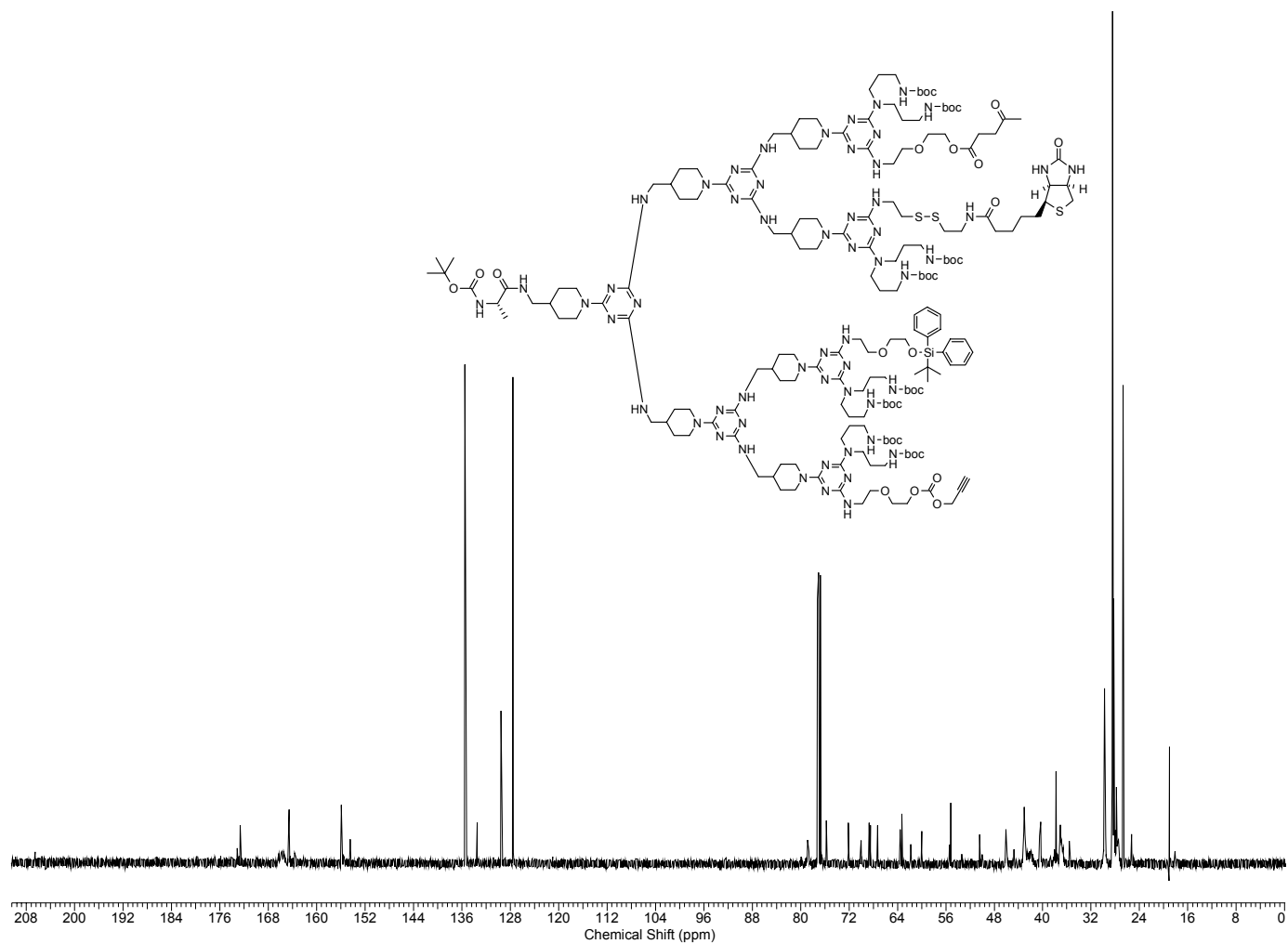
**Figure C.18a.** The  $^1\text{H}$  NMR spectrum of (+) Biotin-PCA. (500 MHz,  $\text{DMSO-}d_6$ )



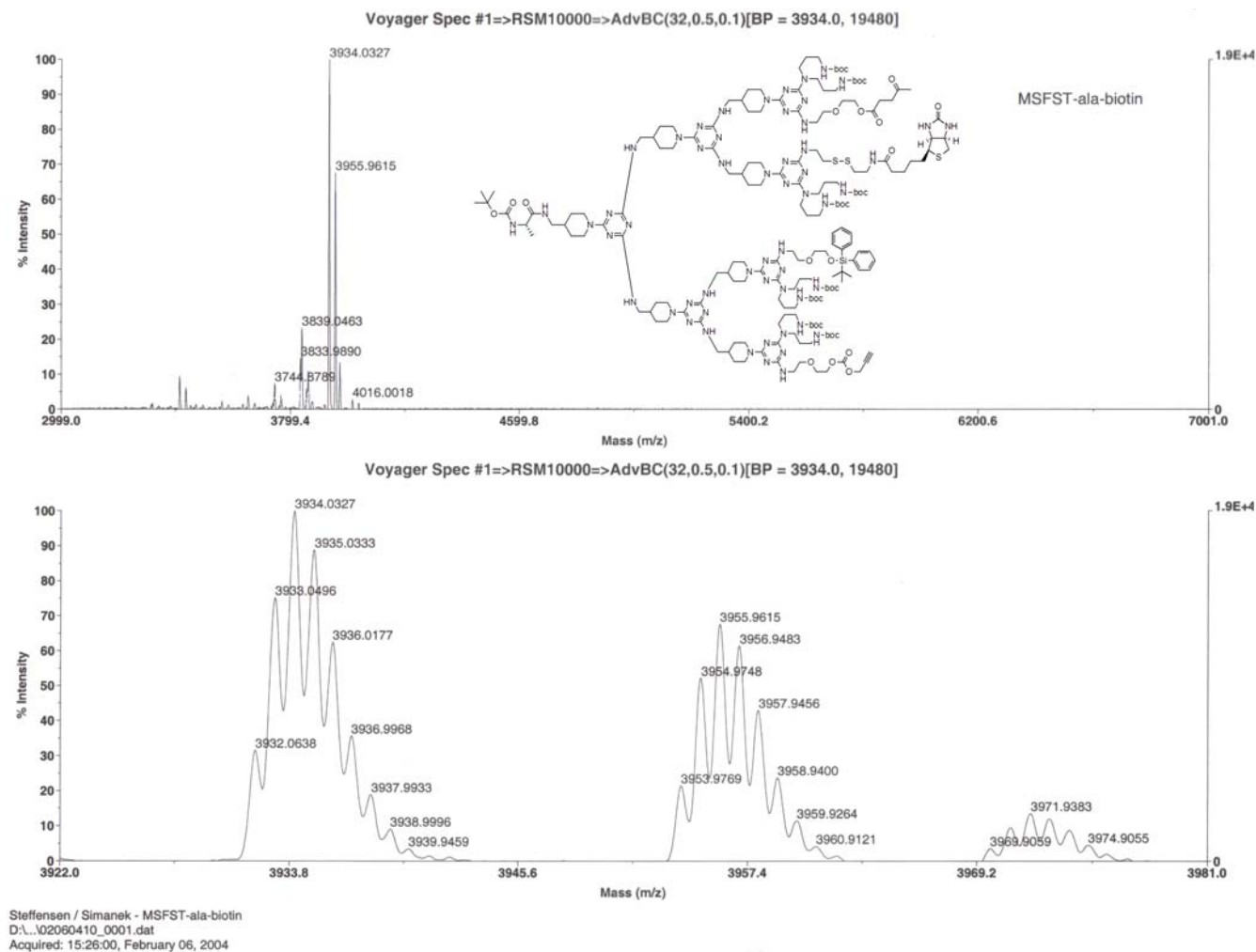
**Figure C.18b.** The  $^{13}\text{C}$  NMR spectrum of (+) Biotin-PCA. (125 MHz, DMSO- $d_6$ )



**Figure C.20a.** The <sup>1</sup>H NMR spectrum of FST-Ala-POC-Biotin, **18**. (500 MHz, CDCl<sub>3</sub>)



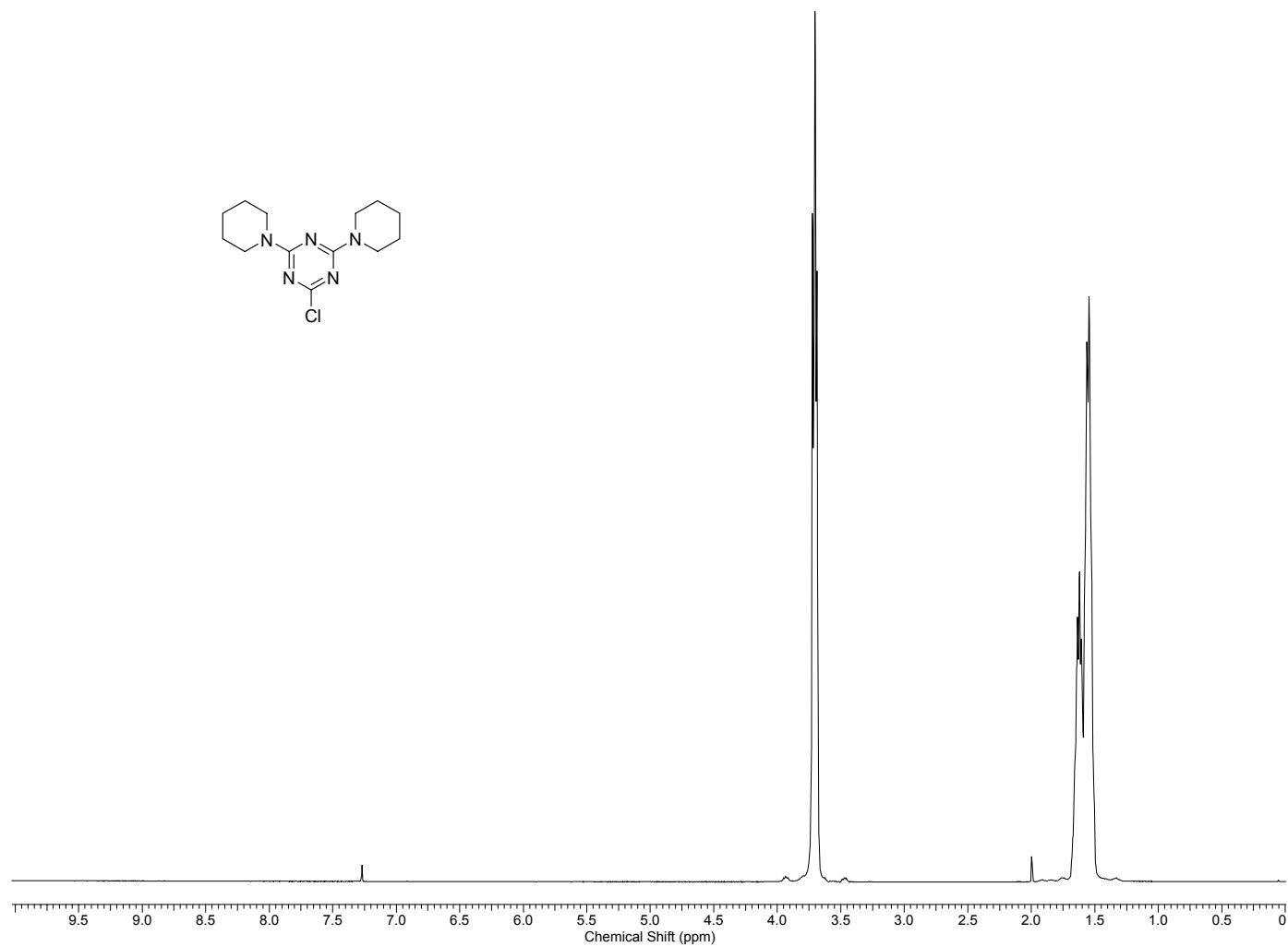
**Figure C.20b.** The  $^{13}\text{C}$  NMR spectrum of FST-Ala-POC-Biotin, **18**. (125 MHz,  $\text{CDCl}_3$ )



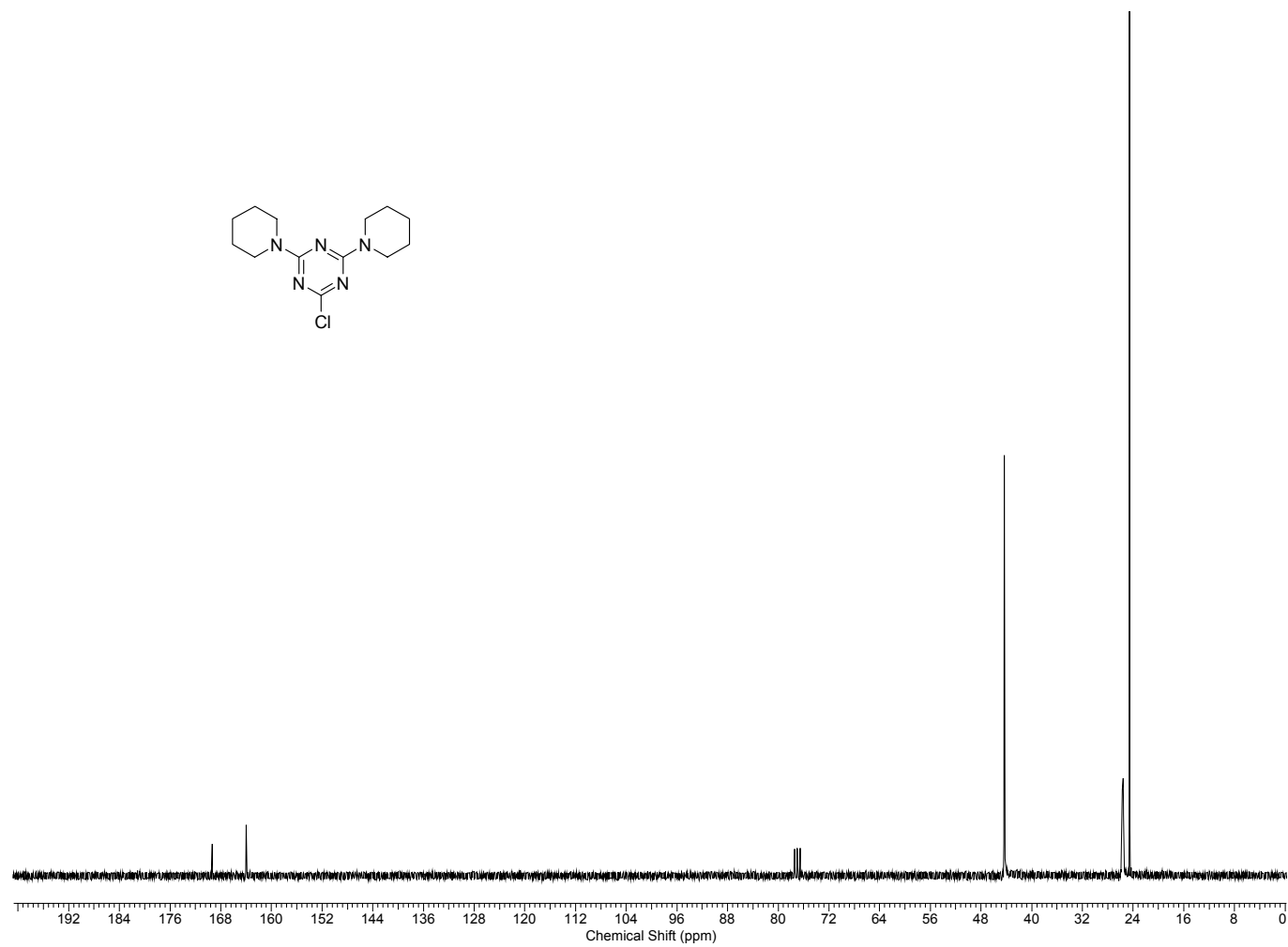
**Figure C.20c.** The MALDI-TOF mass spectrum of FST-Ala-POC-Biotin, **18**.



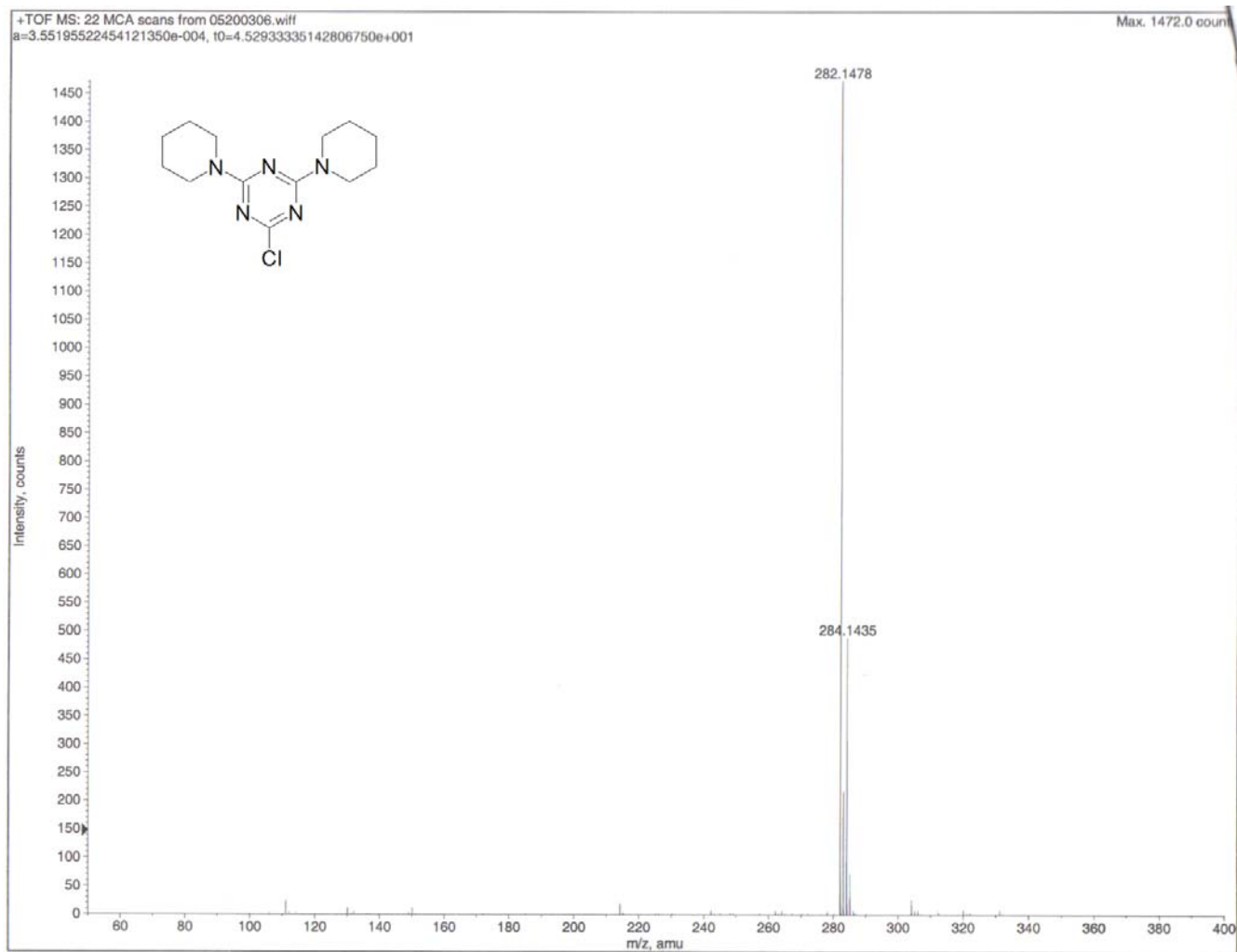
**APPENDIX D**  
**SPECTRA RELEVANT TO CHAPTER IV**



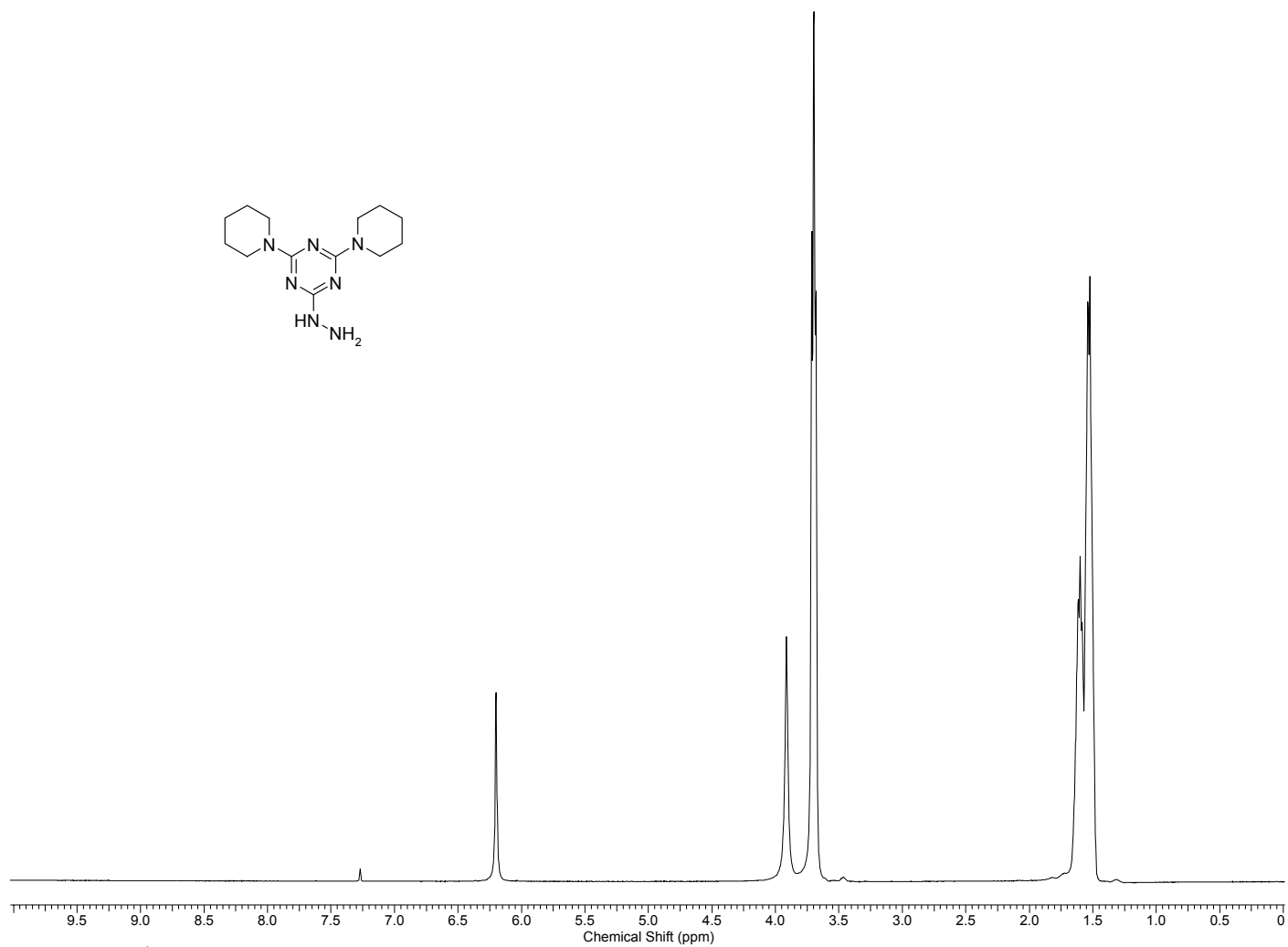
**Figure D.1a.** The  $^1\text{H}$  NMR spectrum of 2-chloro-4,6-di(piperidine-1-yl)-1,3,5-triazine, **1**. (300 MHz,  $\text{CDCl}_3$ )



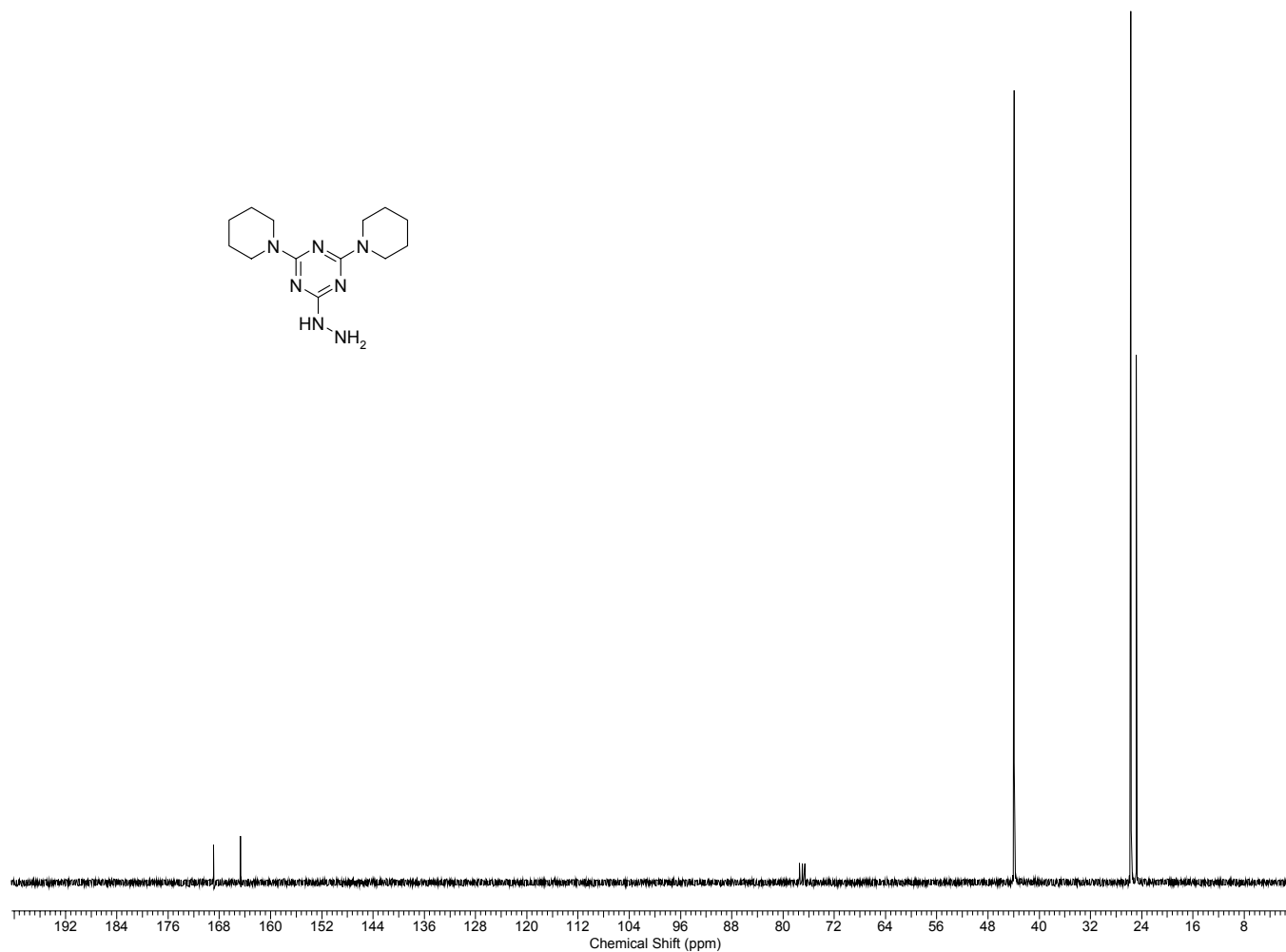
**Figure D.1b.** The  $^{13}\text{C}$  NMR spectrum of 2-chloro-4,6-di(piperidine-1-yl)-1,3,5-triazine, **1**. (75 MHz,  $\text{CDCl}_3$ )



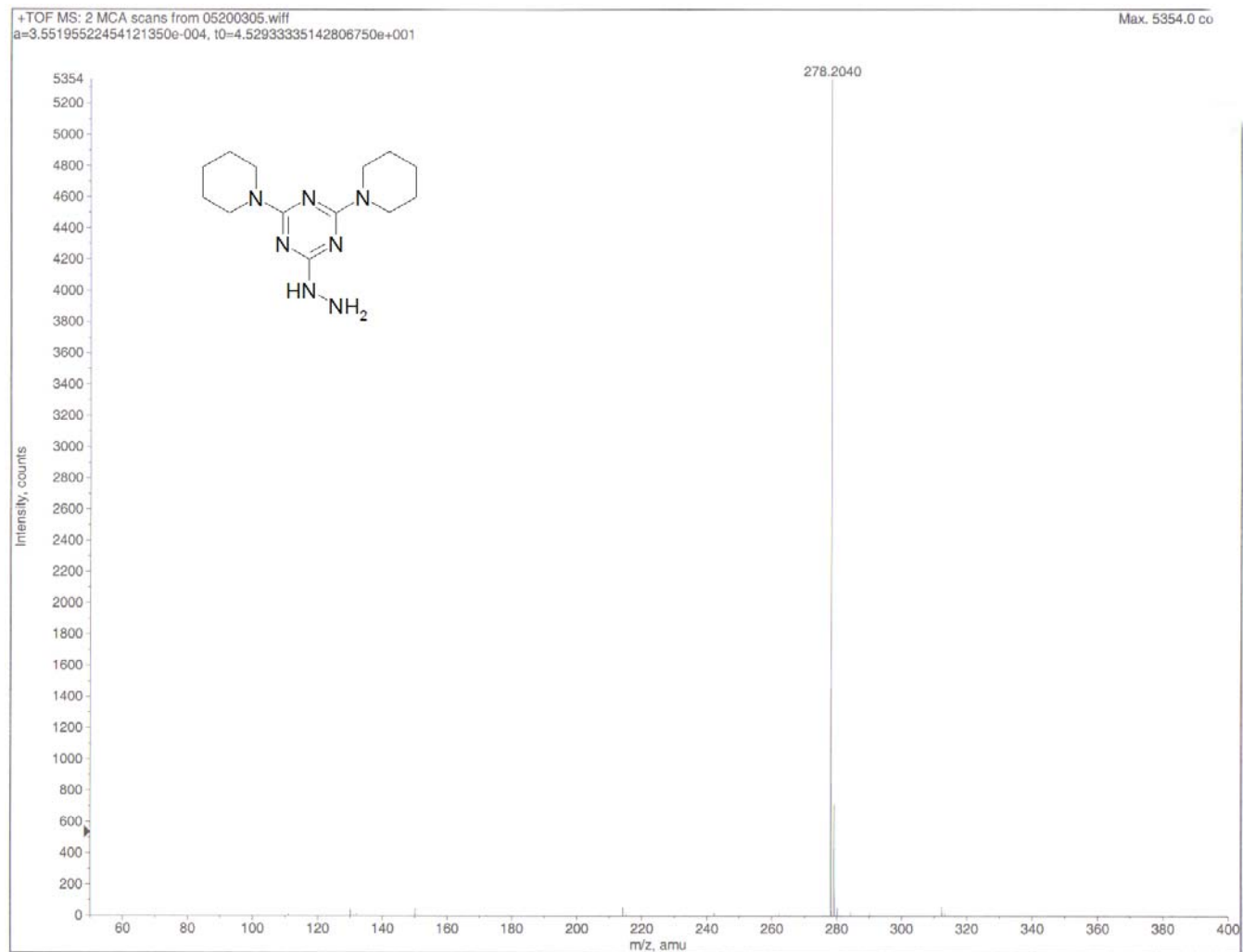
**Figure D.1c.** The ESI-TOF mass spectrum 2-chloro-4,6-di(piperidine-1-yl)-1,3,5-triazine, **1**.



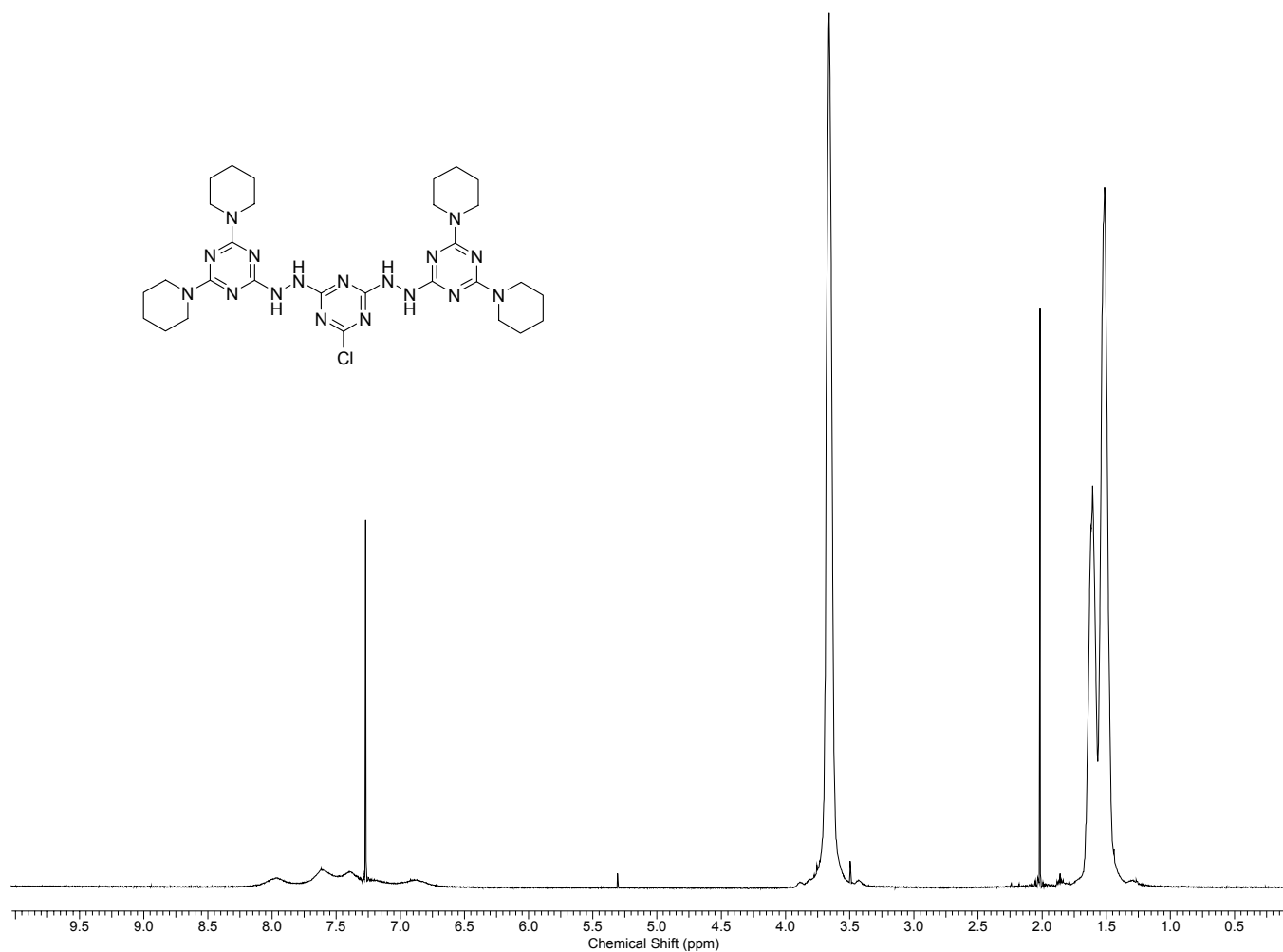
**Figure D.2a.** The <sup>1</sup>H NMR spectrum of 1-(4,6-di(piperidine-1-yl)-1,3,5-triazine-2-yl)hydrazine, **2**. (300 MHz, CDCl<sub>3</sub>)



**Figure D.2b.** The <sup>13</sup>C NMR spectrum of 1-(4,6-di(piperidine-1-yl)-1,3,5-triazine-2-yl)hydrazine, **2**. (300 MHz, CDCl<sub>3</sub>)

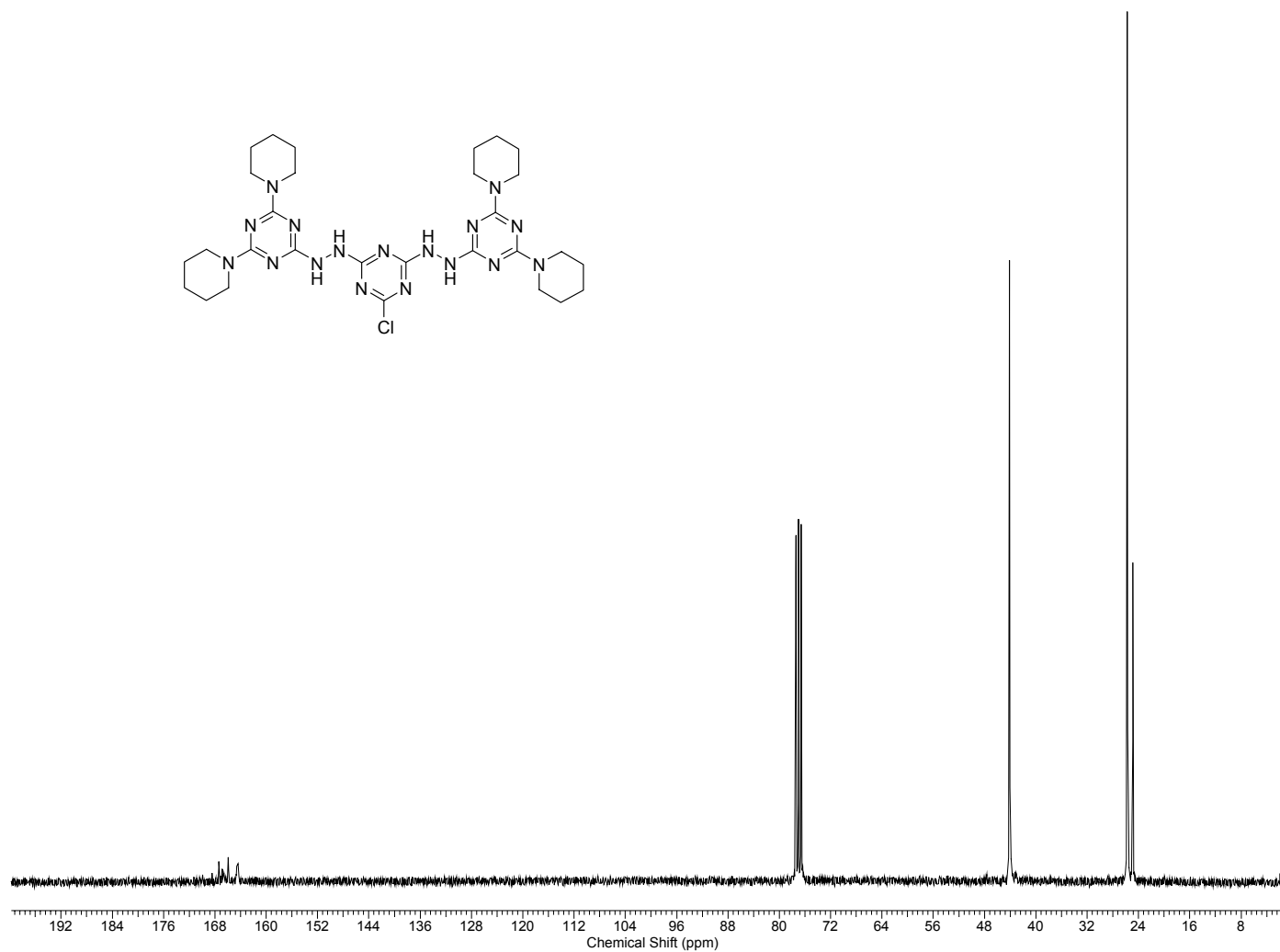


**Figure D.2c.** The ESI-TOF mass spectrum of 1-(4,6-di(piperidine-1-yl)-1,3,5-triazine-2-yl)hydrazine, **2**.

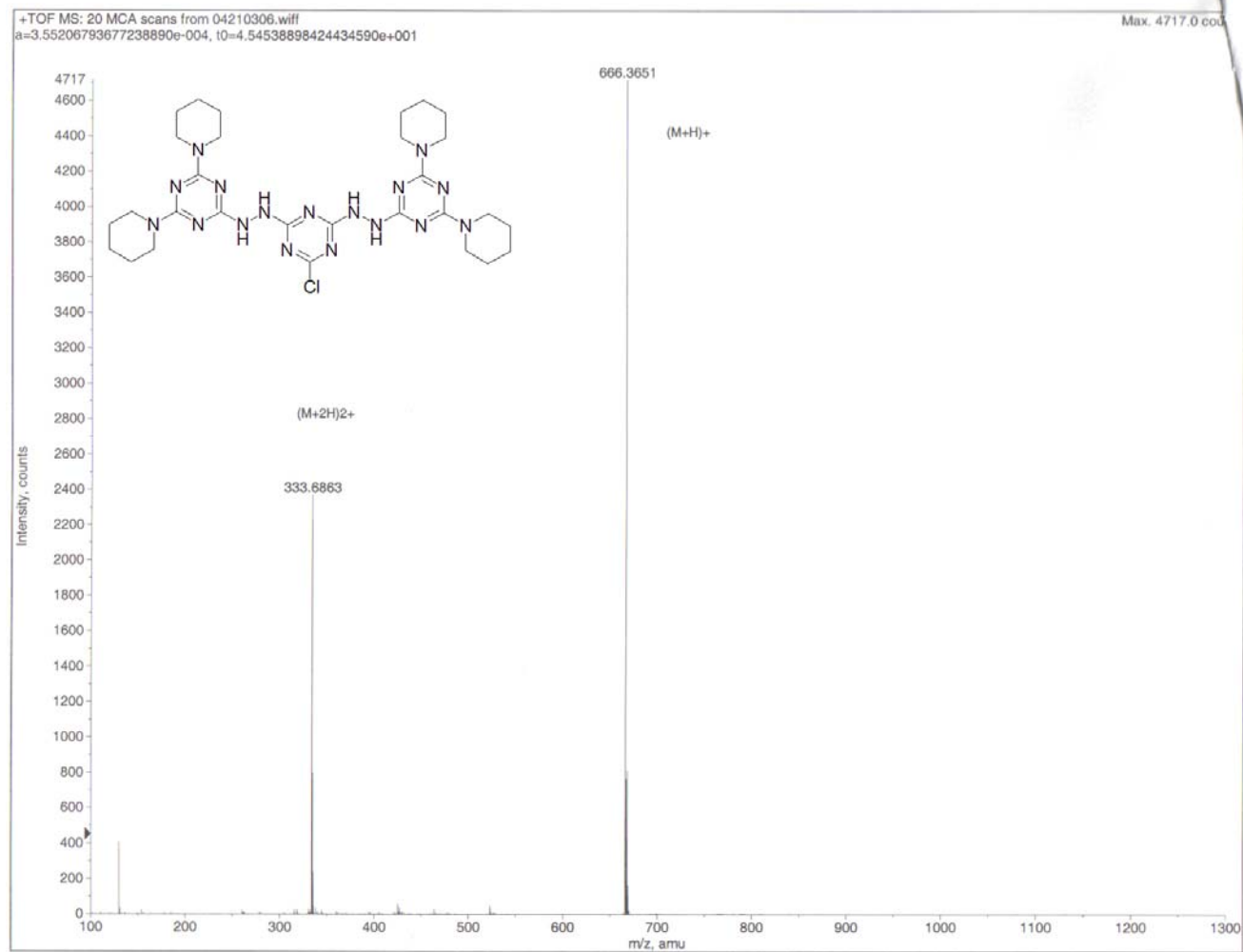


**Figure D.3a.** The  $^1\text{H}$  NMR spectrum of dendron **3**. (300 MHz,  $\text{CDCl}_3$ )

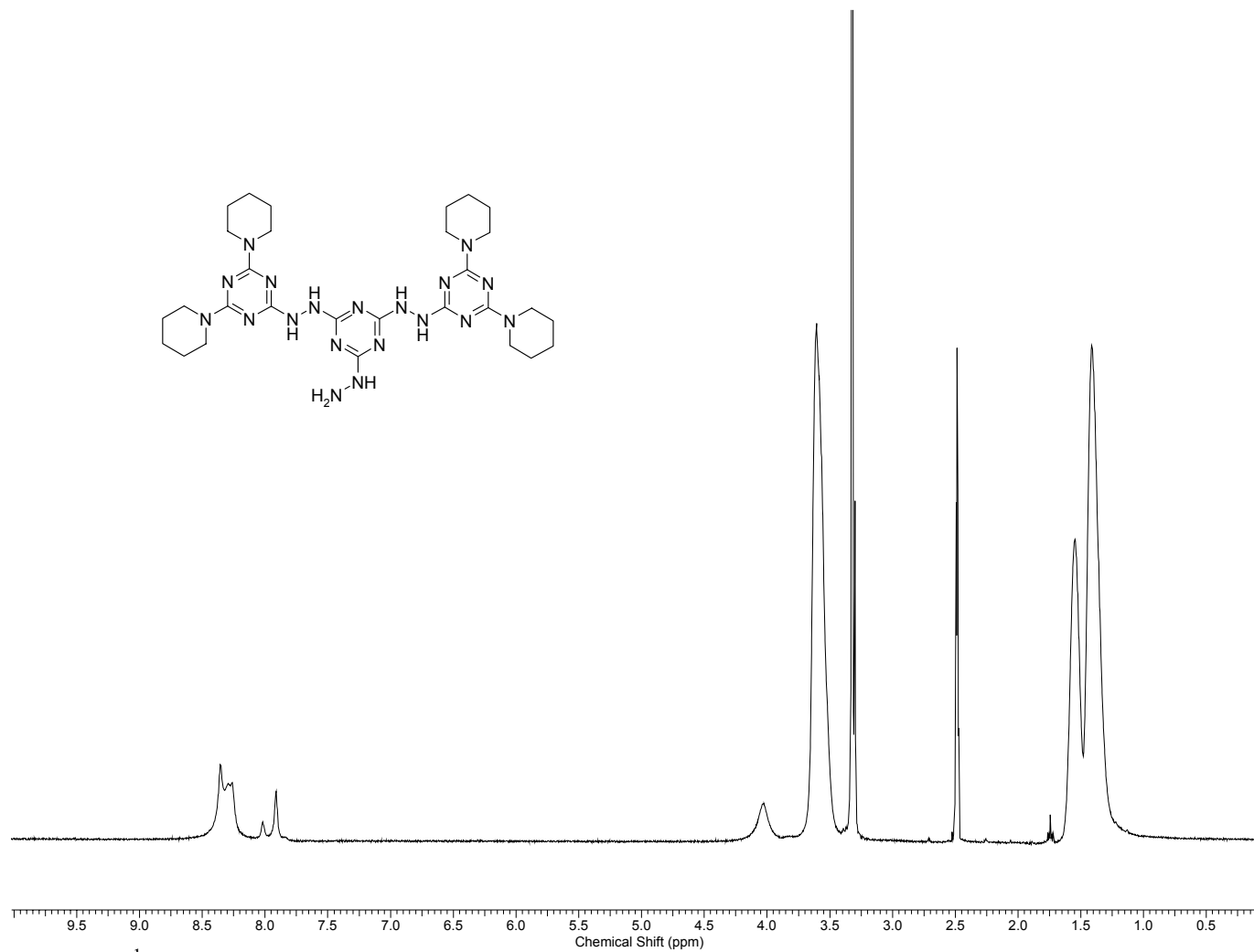




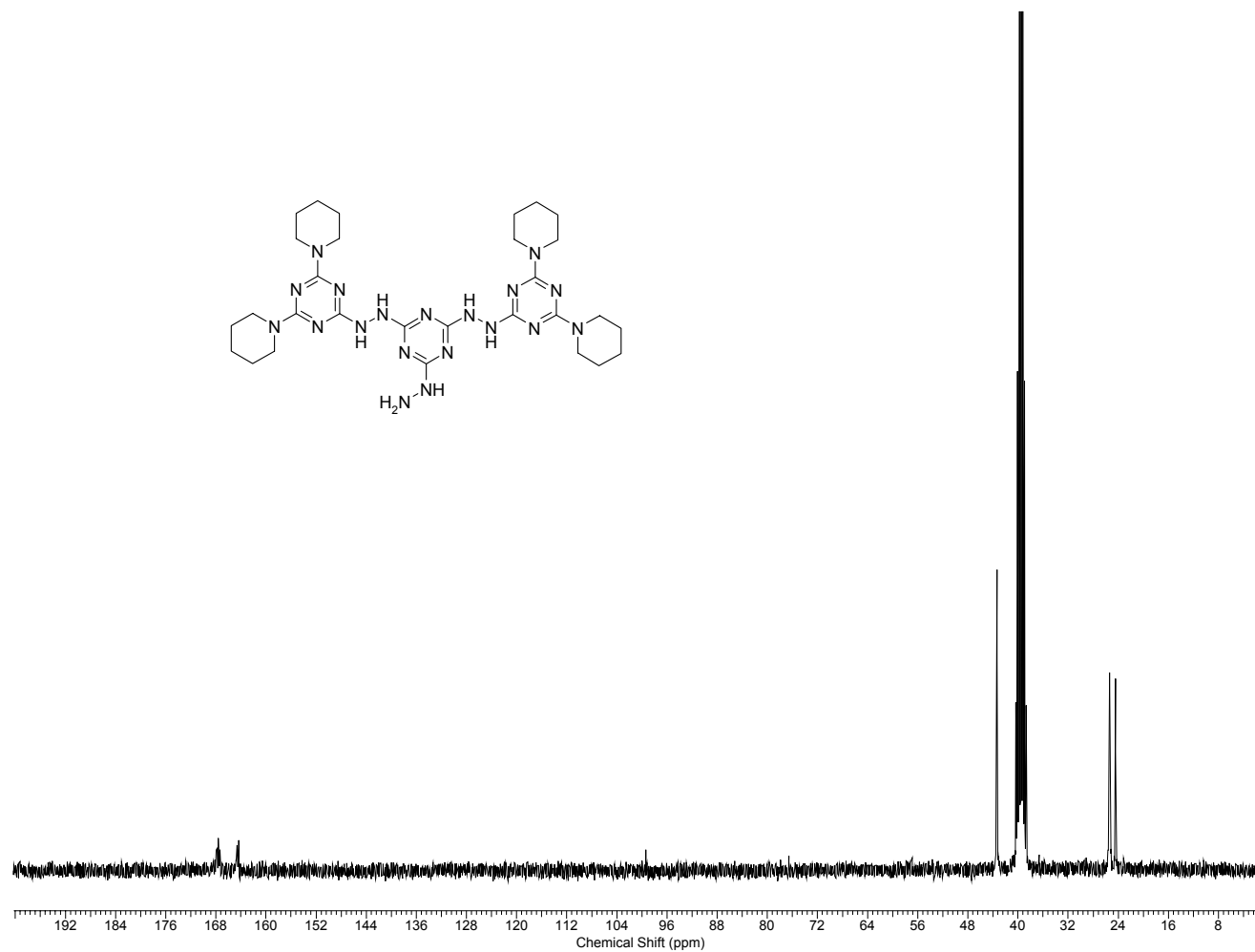
**Figure D.3b.** The  $^{13}\text{C}$  NMR spectrum of dendron 3. (75 MHz,  $\text{CDCl}_3$ )



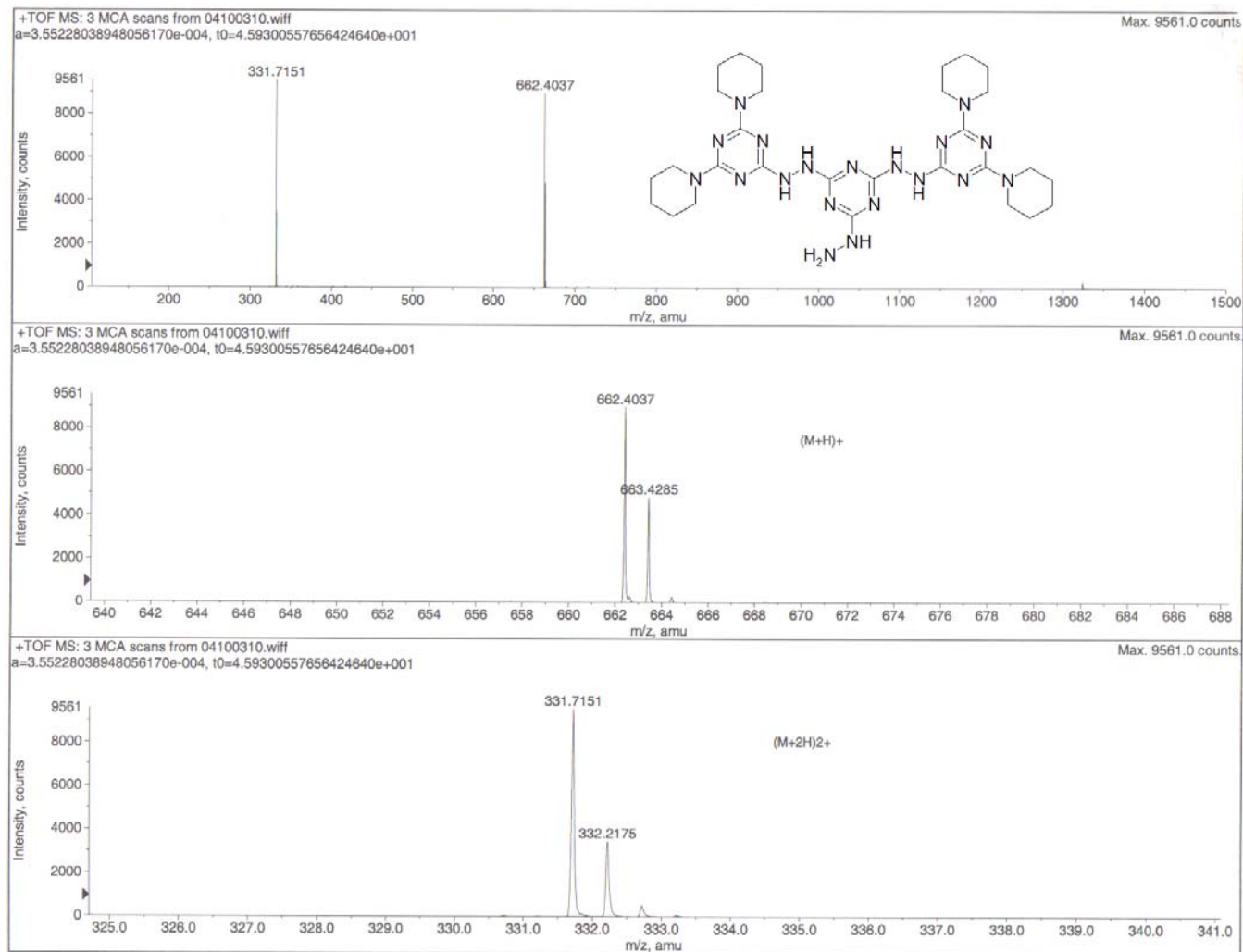
**Figure D.3c.** The ESI-TOF mass spectrum of dendron 3.



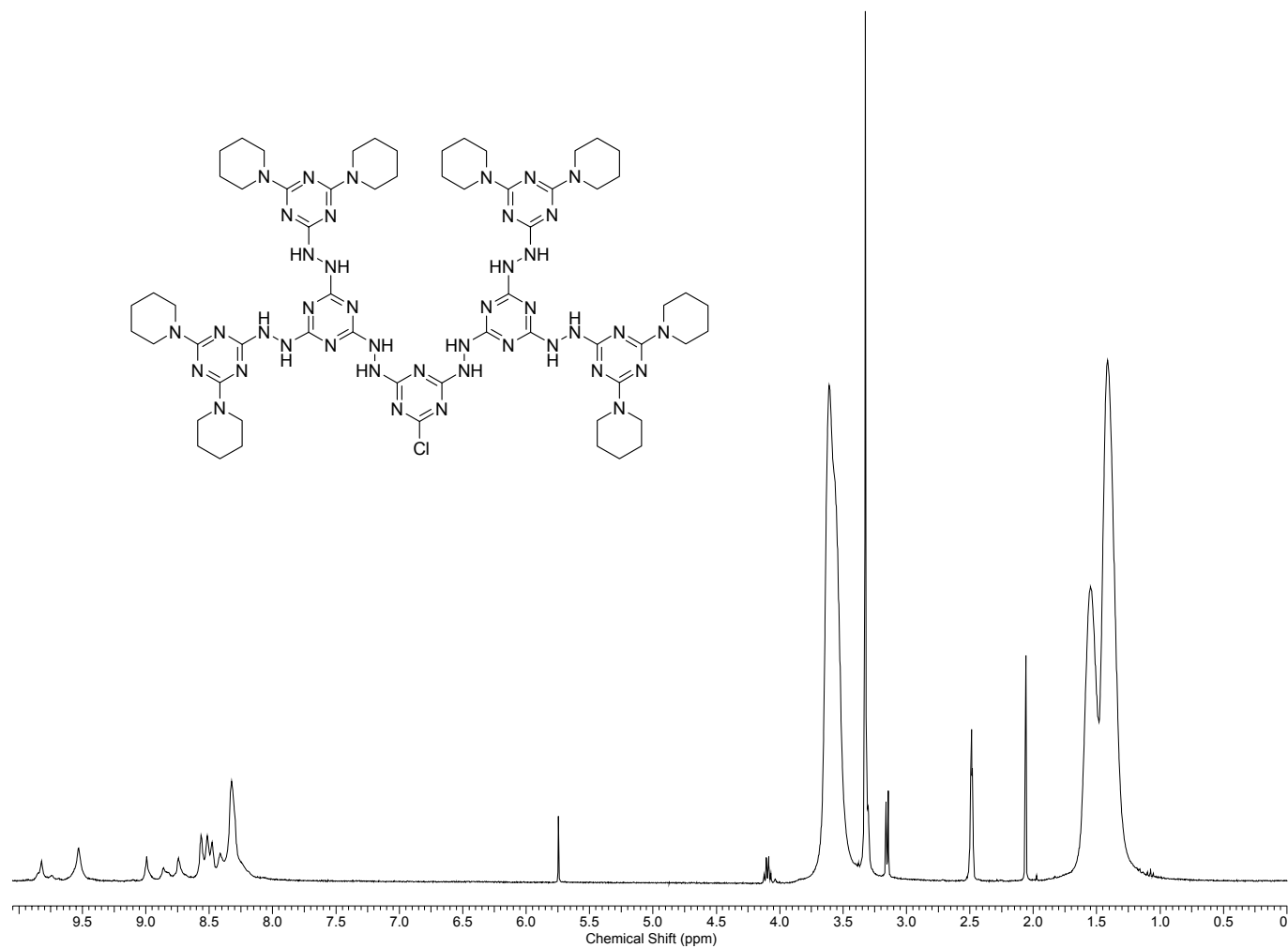
**Figure D.4a.** The  $^1\text{H}$  NMR spectrum of dendron 4. (300 MHz,  $\text{DMSO}-d_6$ )



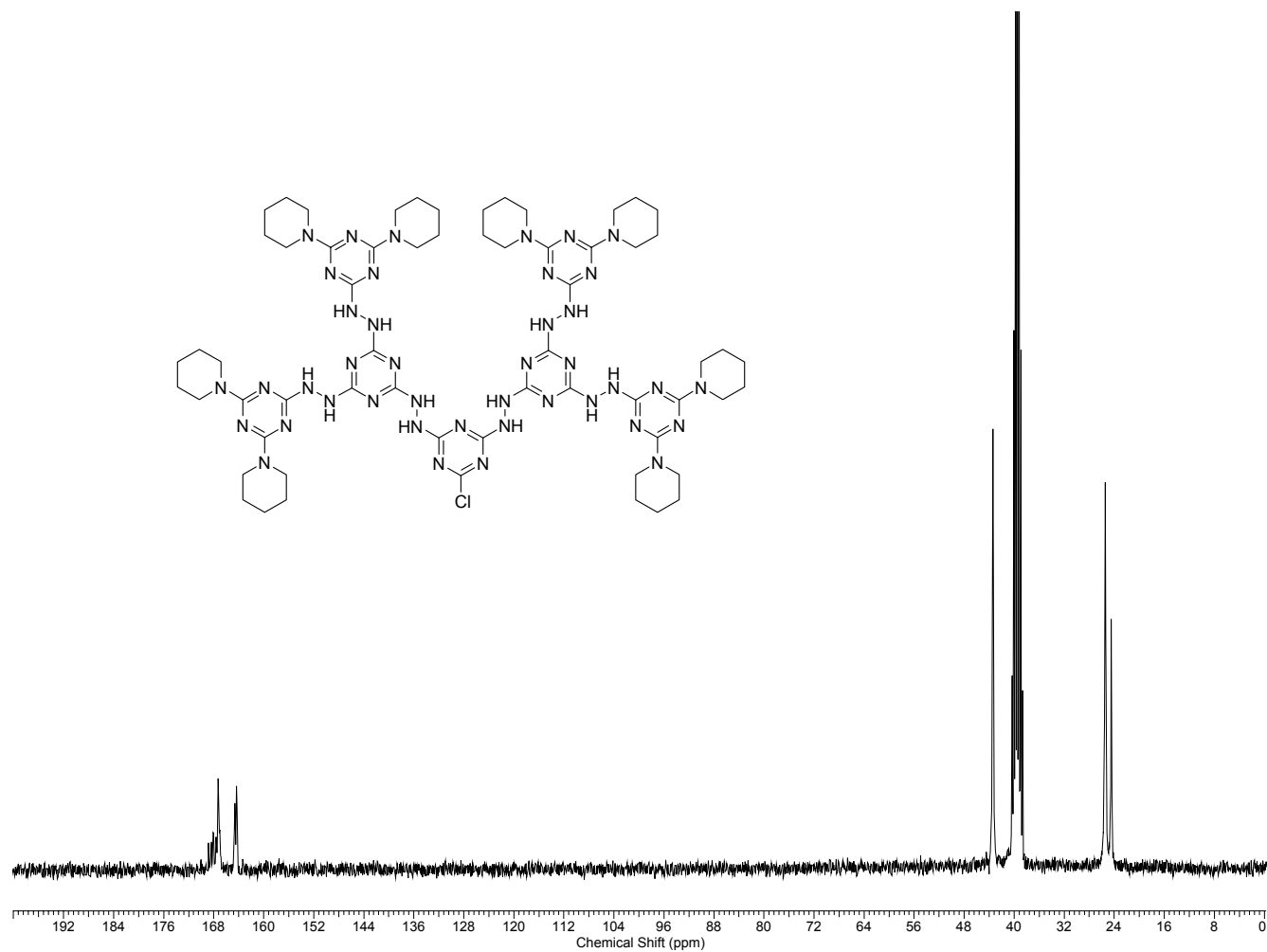
**Figure D.4b.** The  $^{13}\text{C}$  NMR spectrum of dendron 4. (75 MHz,  $\text{DMSO}-d_6$ )



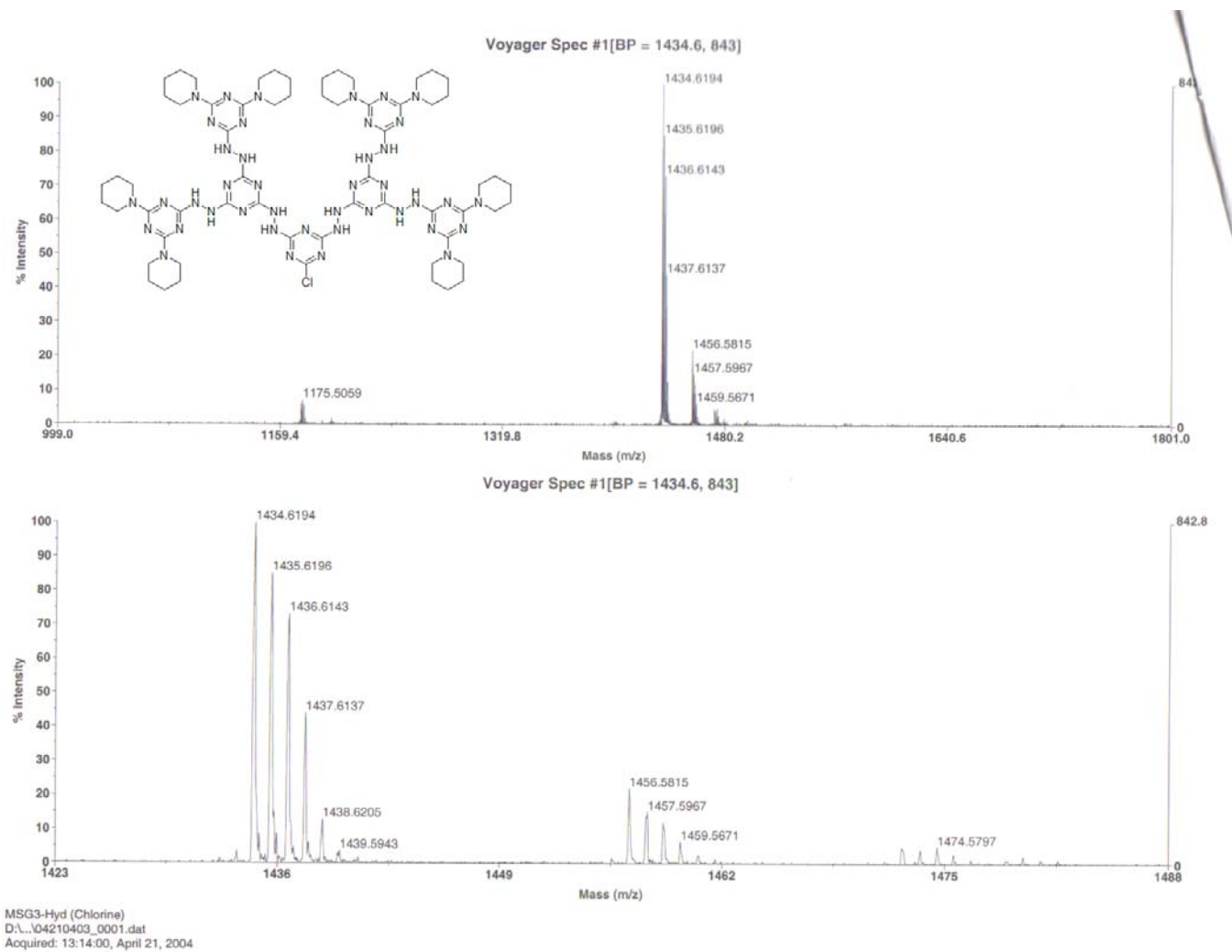
**Figure D.4c.** The ESI-TOF mass spectrum of dendron **4**.



**Figure D.5a.** The  $^1\text{H}$  NMR spectrum of dendron **5**. (300 MHz,  $\text{DMSO}-d_6$ )

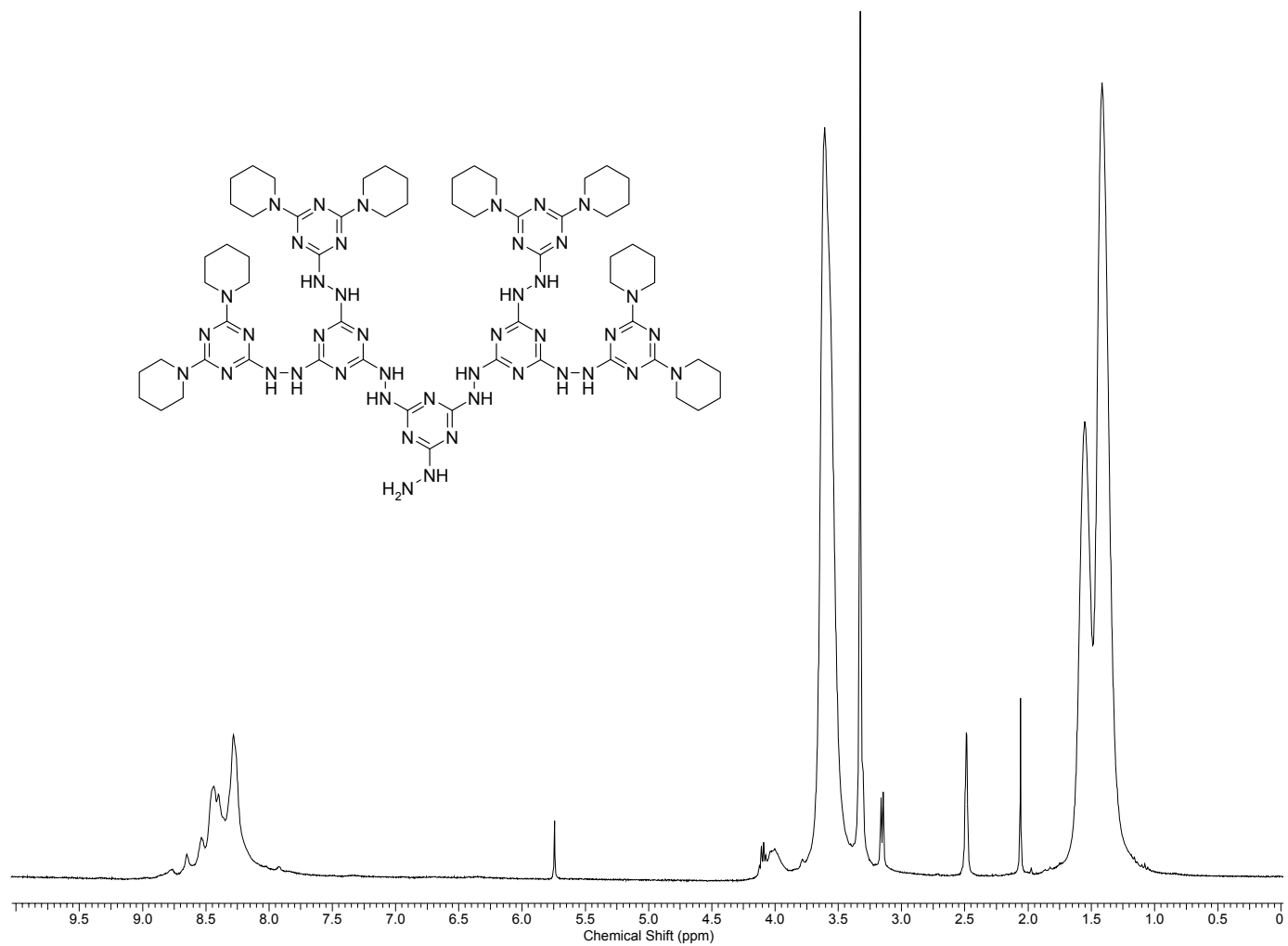


**Figure D.5b.** The  $^{13}\text{C}$  NMR spectrum of dendron 5. (75 MHz,  $\text{DMSO}-d_6$ )

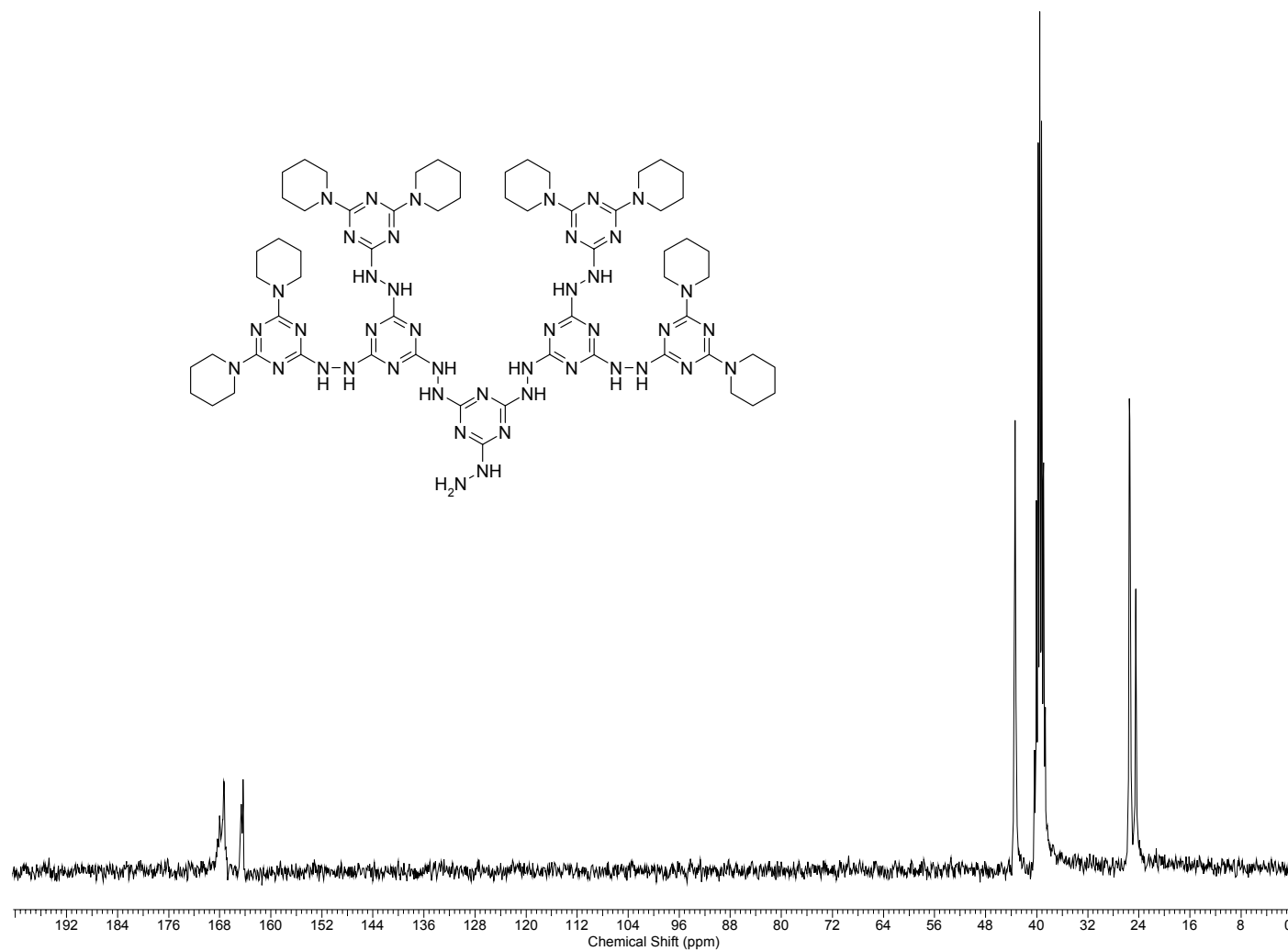


**Figure D.5c.** The MALDI-TOF mass spectrum of dendron 5.

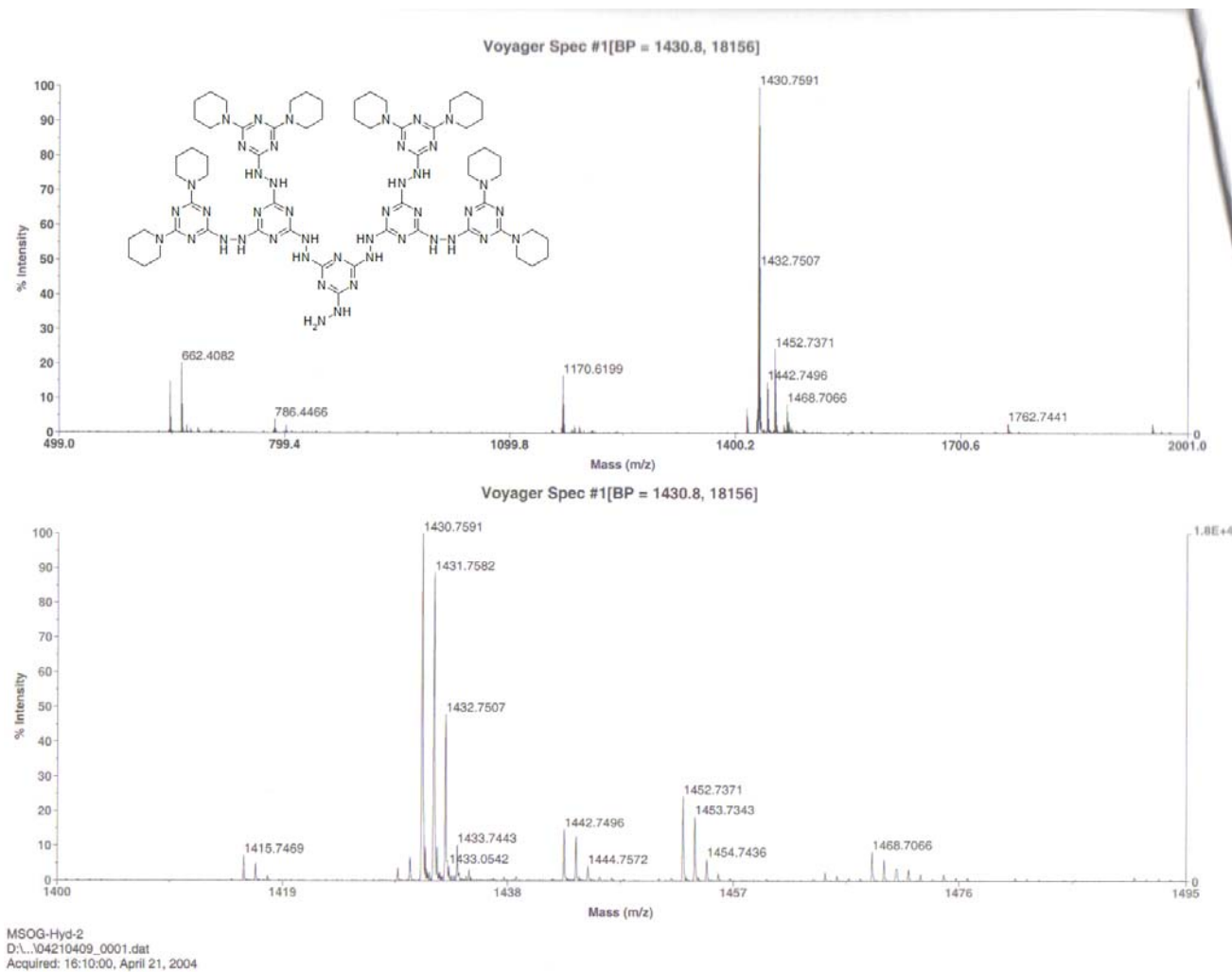




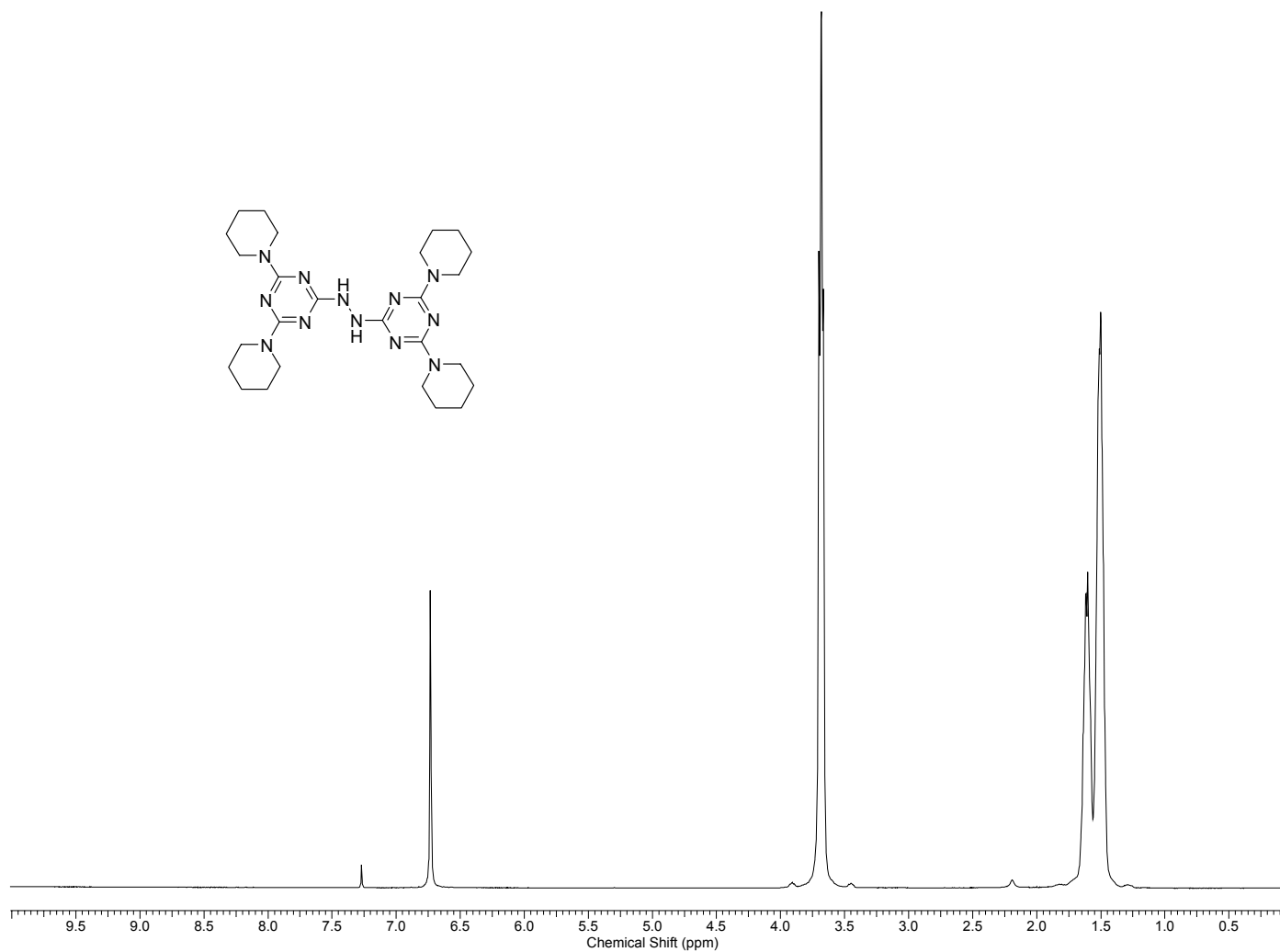
**Figure D.6a.** The  $^1\text{H}$  NMR spectrum of dendron 6. (300 MHz,  $\text{DMSO}-d_6$ )



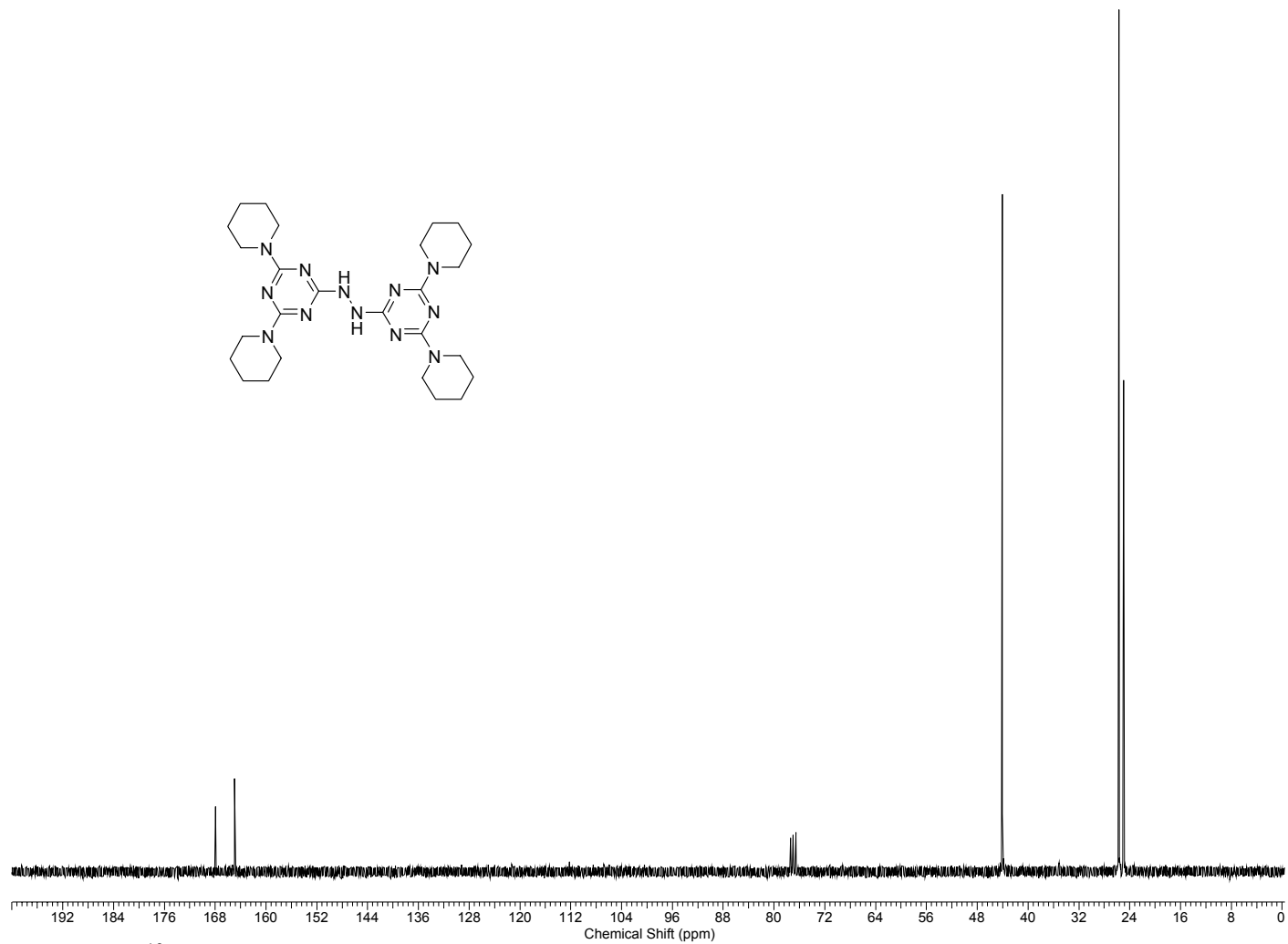
**Figure D.6b.** The  $^{13}\text{C}$  NMR spectrum of dendron 6. (75 MHz,  $\text{DMSO}-d_6$ )



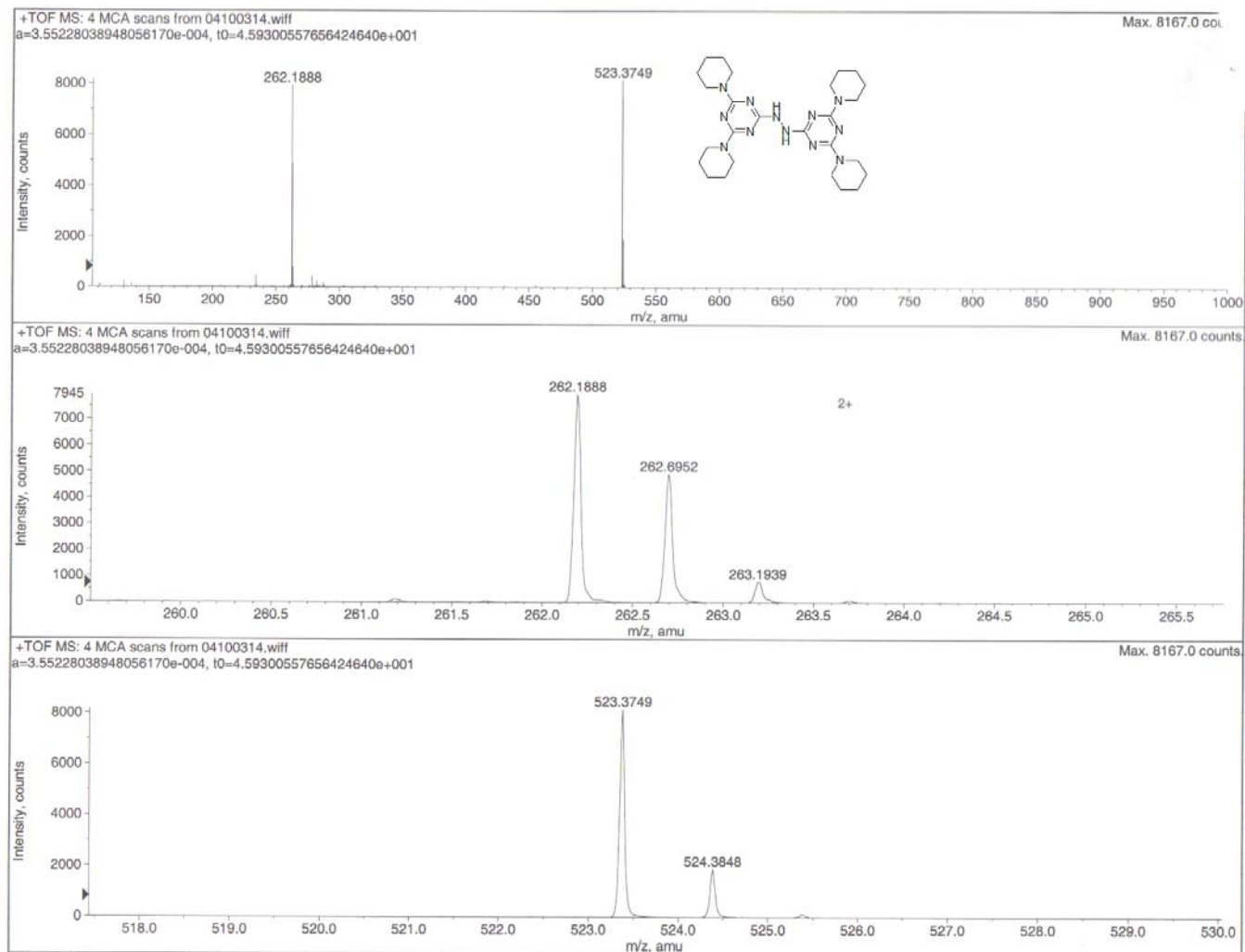
**Figure D.6c.** The MALDI-TOF mass spectrum of dendron 6.

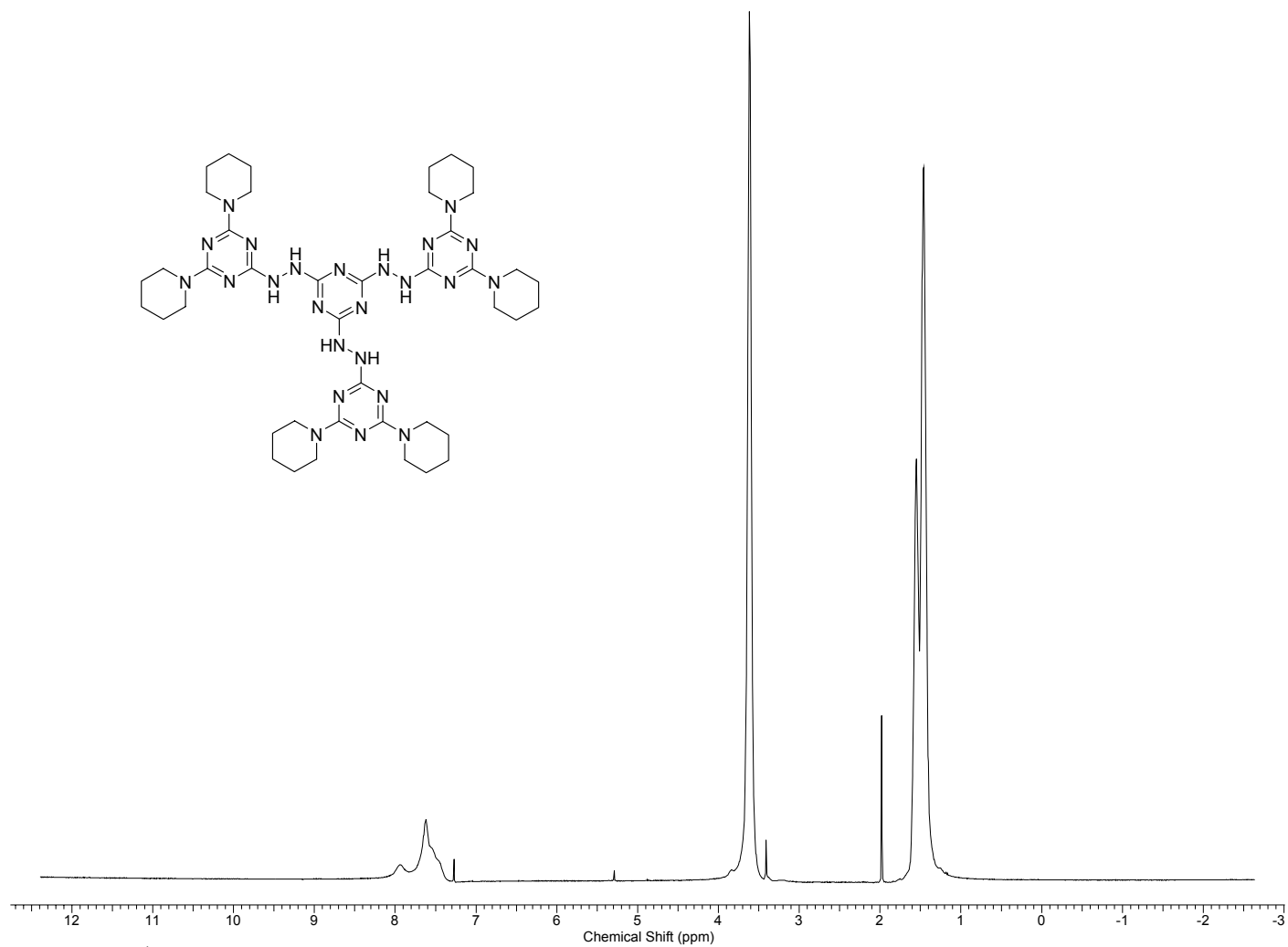


**Figure D.7a.** The  $^1\text{H}$  NMR spectrum of dendrimer 7 (G1-dimer). (300 MHz.  $\text{CDCl}_3$ )

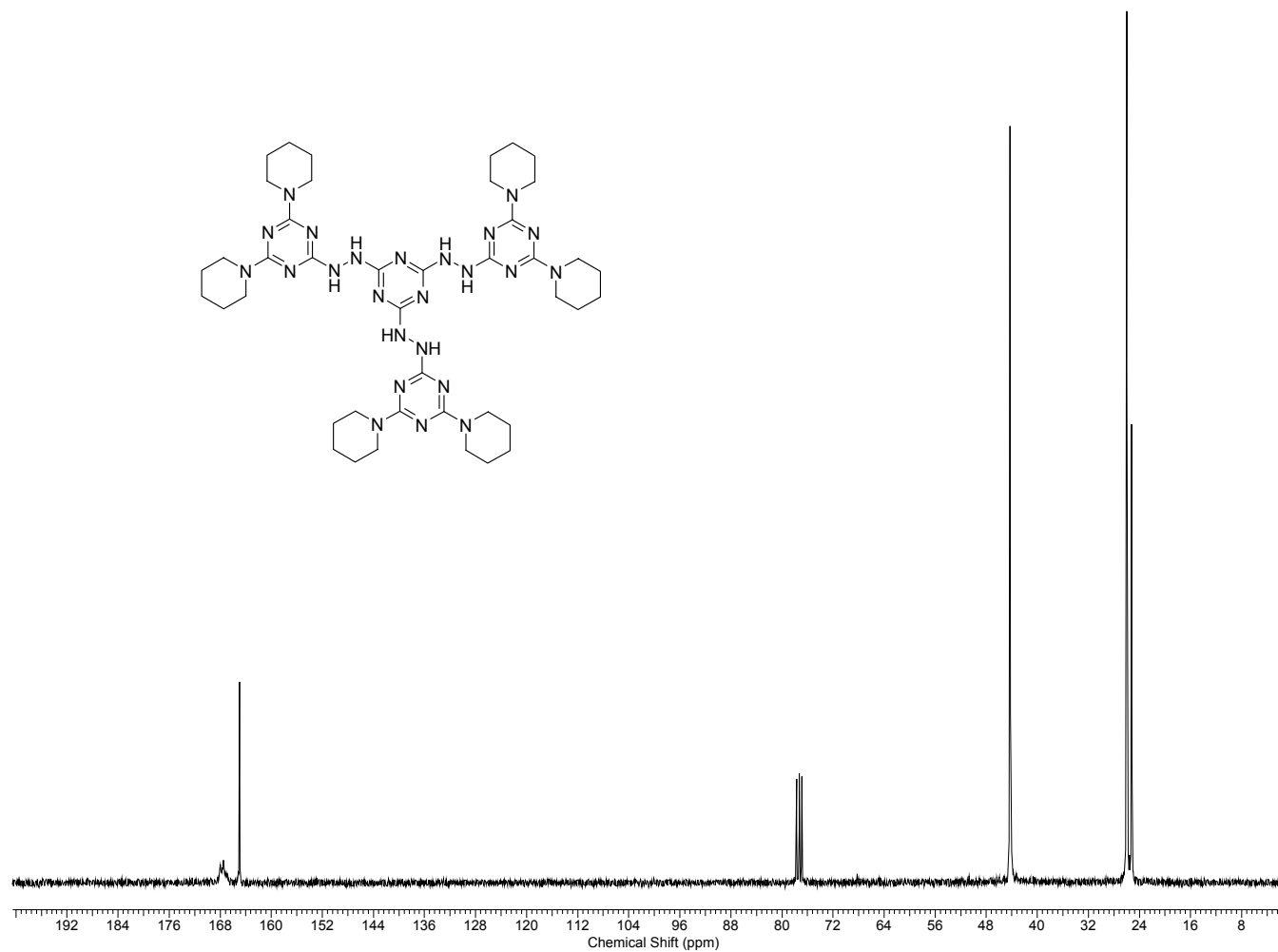


**Figure D.7b.** The  $^{13}\text{C}$  NMR spectrum of dendrimer 7 (G1-dimer). (75 MHz,  $\text{CDCl}_3$ )



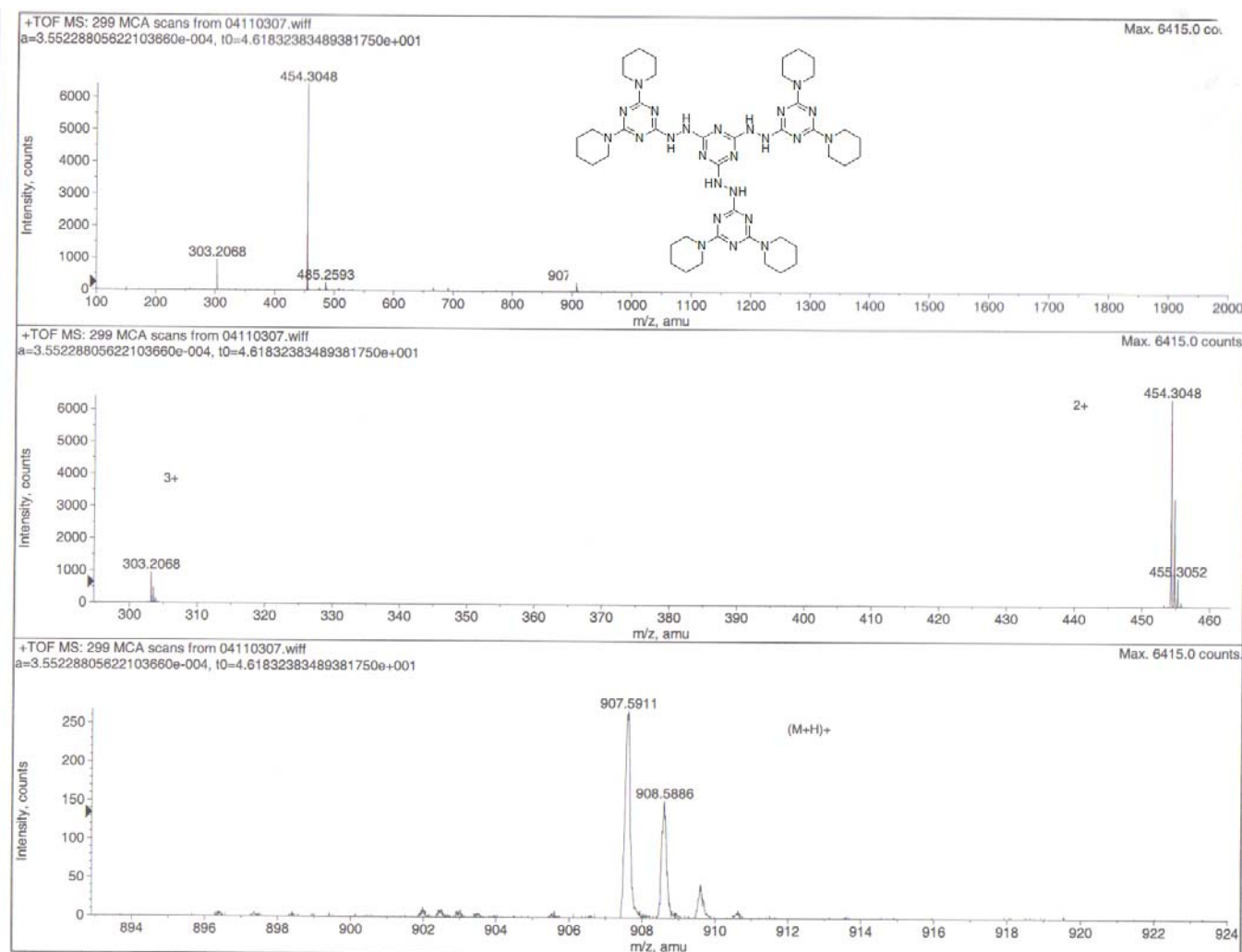


**Figure D.8a.** The  $^1\text{H}$  NMR spectrum of dendrimer **8** (G1-trimer). (300 MHz,  $\text{CDCl}_3$ )

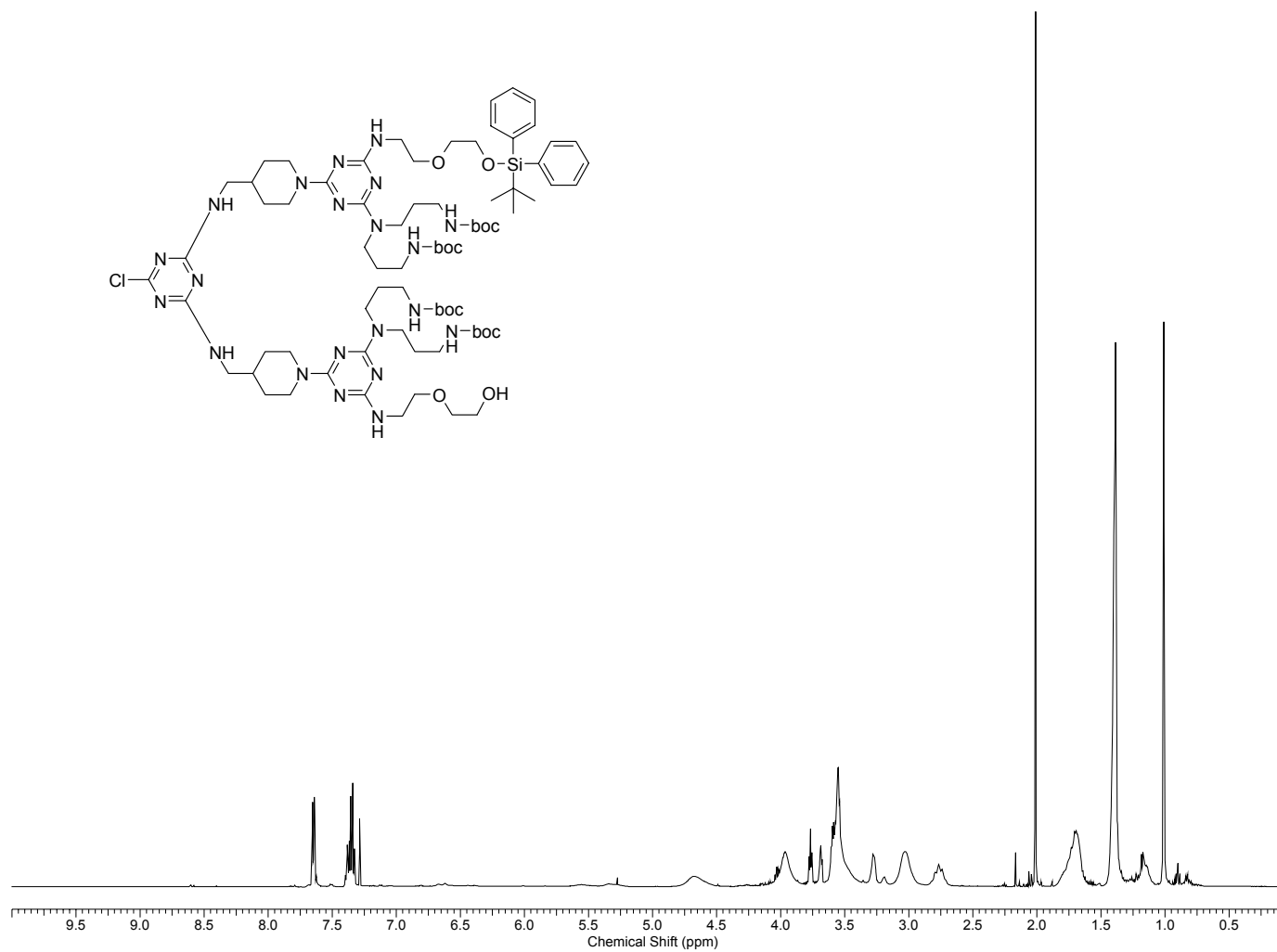


**Figure D.8b.** The  $^{13}\text{C}$  NMR spectrum of dendrimer **8** (G1-trimer). (75 MHz,  $\text{CDCl}_3$ )

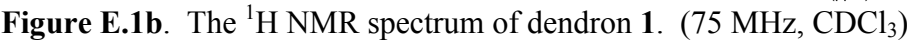


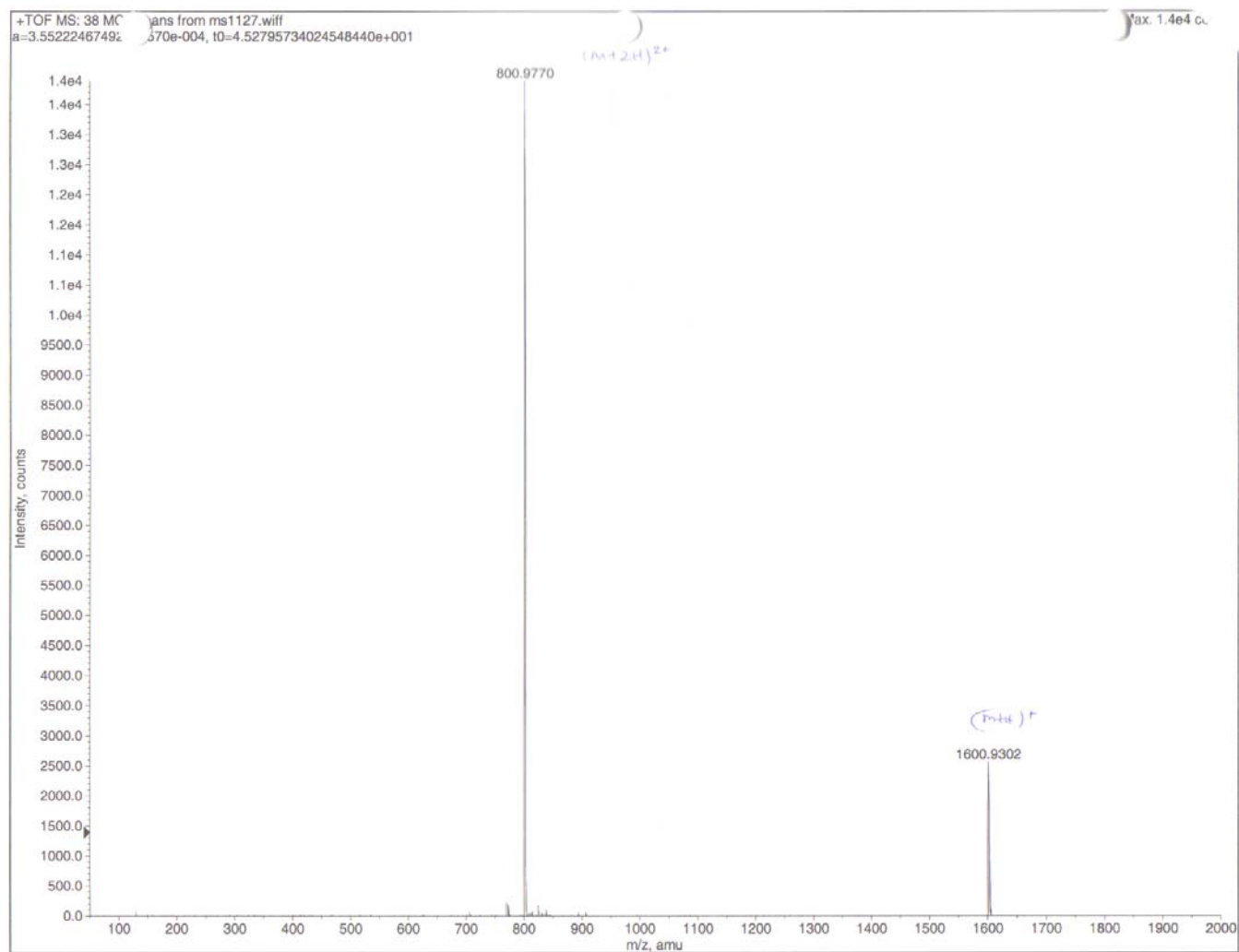


**APPENDIX E**  
**SPECTRA RELEVANT TO CHAPTER V**

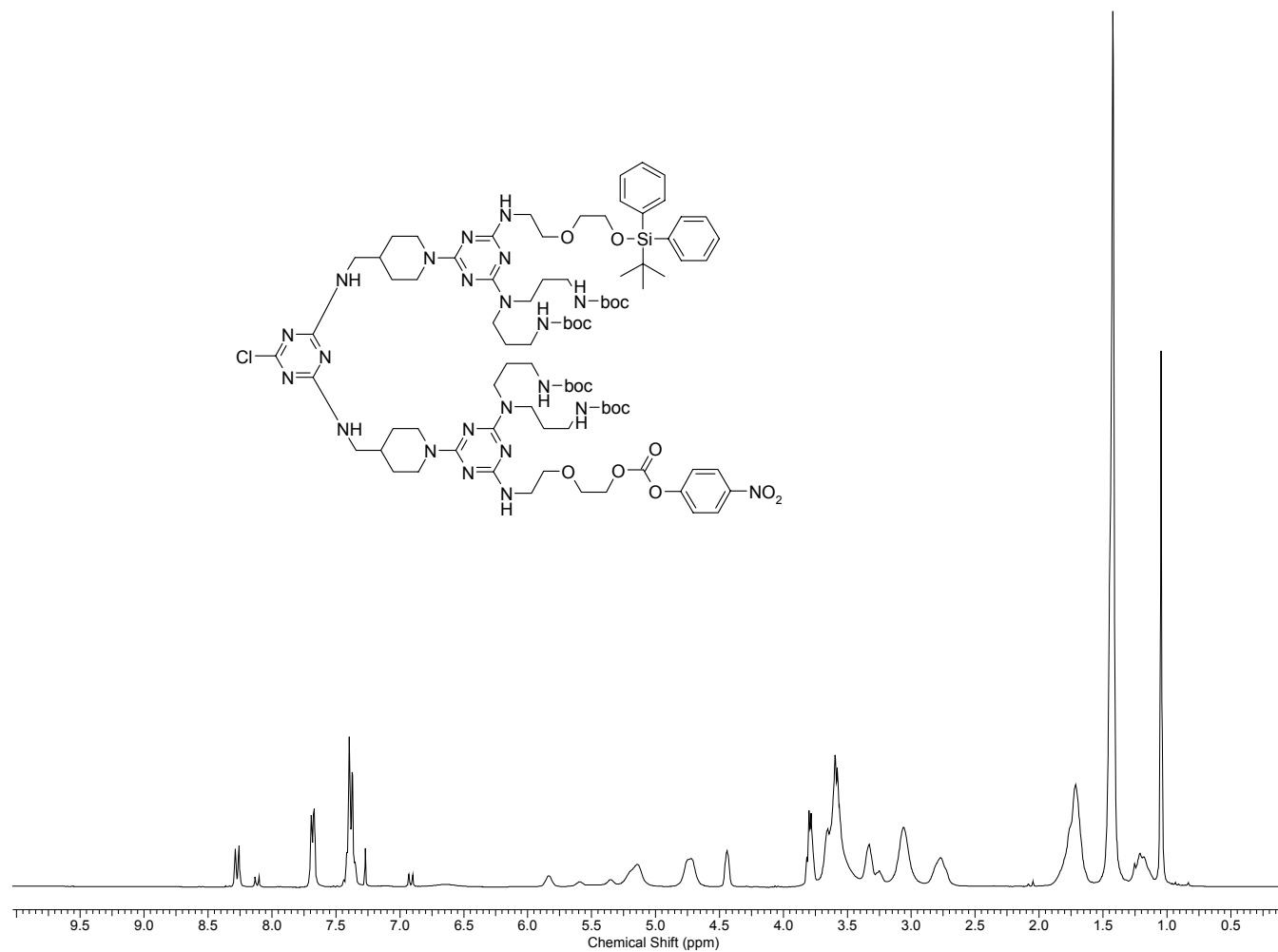


**Figure E.1a.** The  $^1\text{H}$  NMR spectrum of dendron 1. (300 MHz,  $\text{CDCl}_3$ )

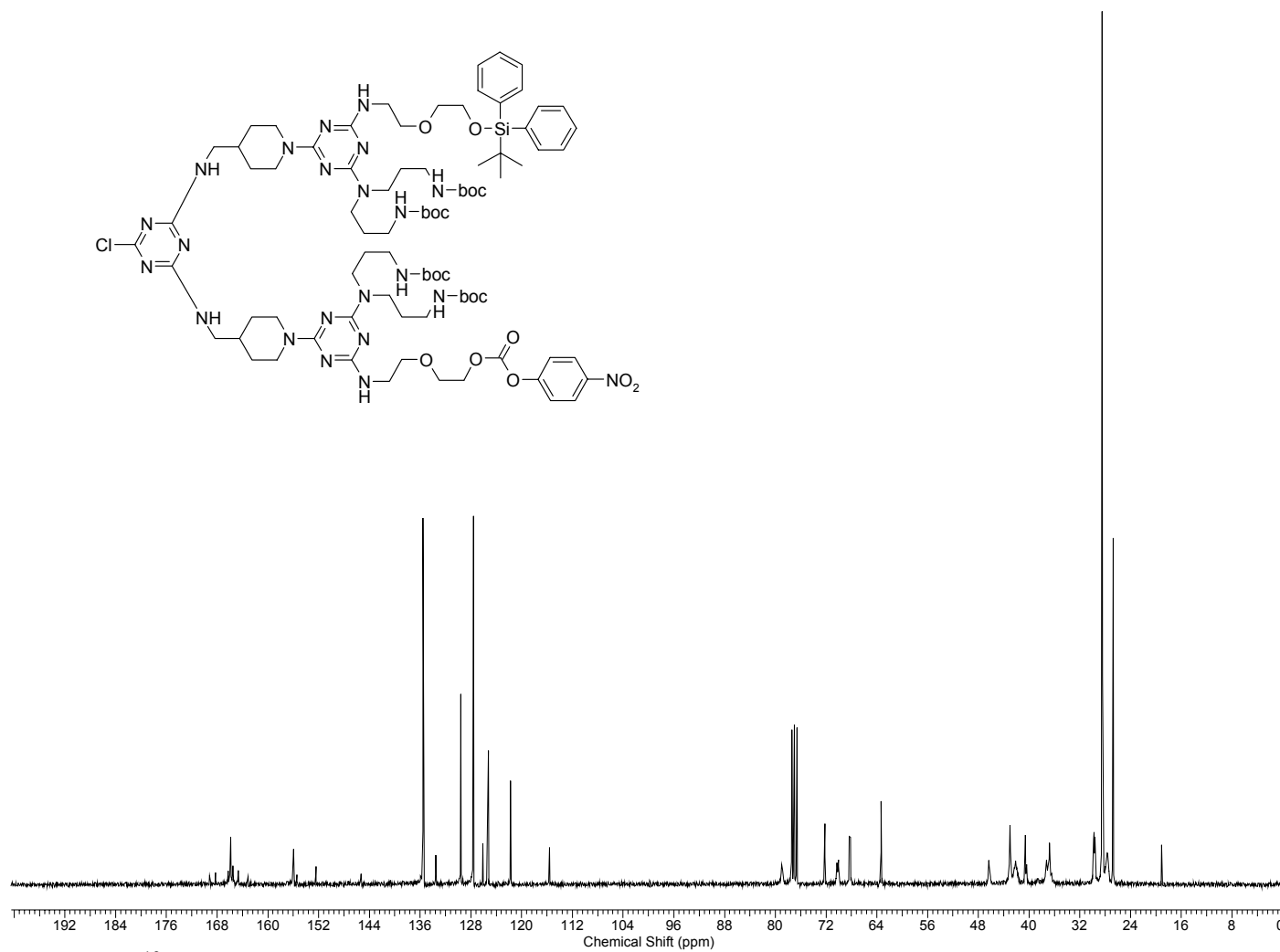




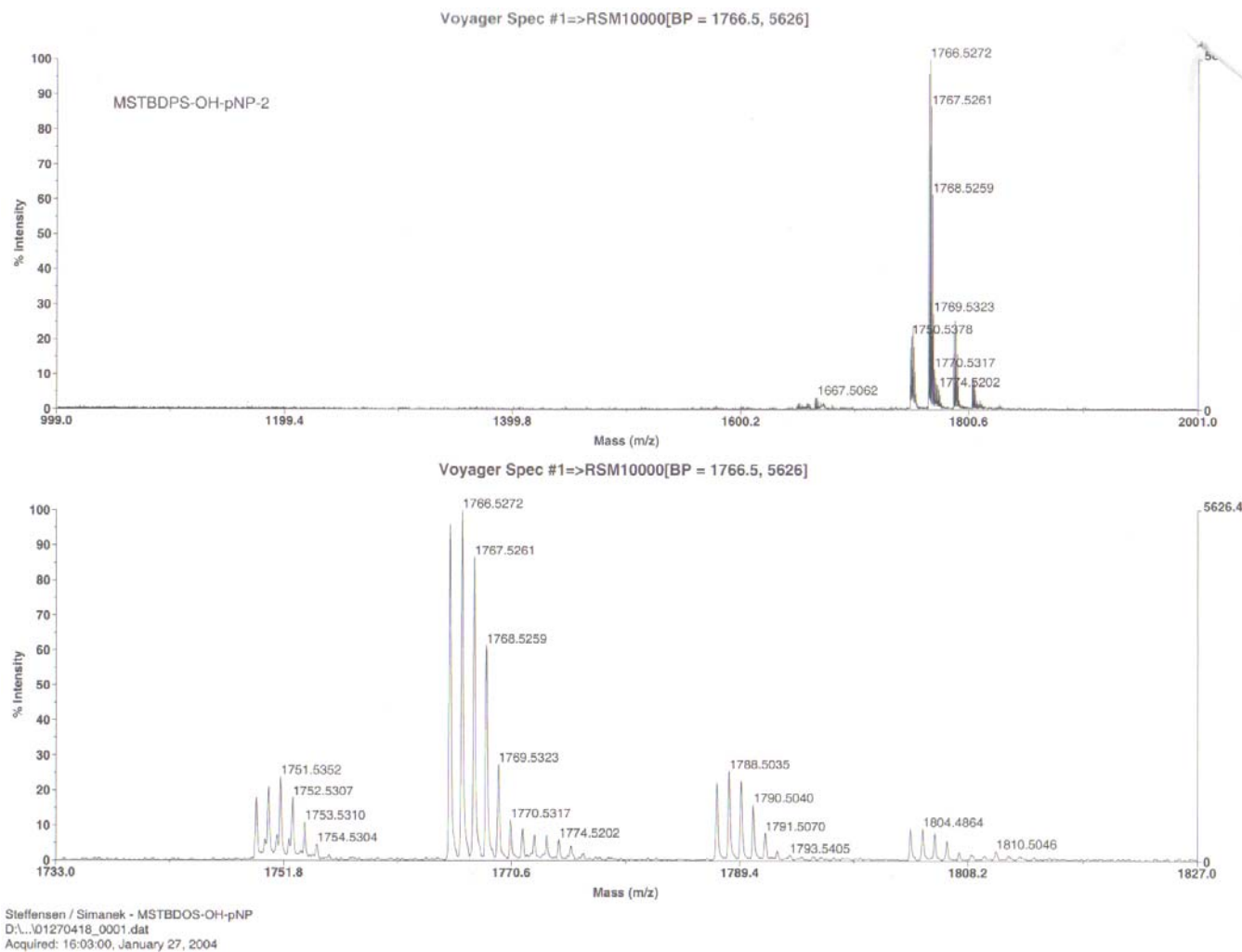
**Figure E.1c.** The ESI-TOF mass spectrum of dendron 1.



**Figure E.2a.** The  $^1\text{H}$  NMR spectrum of dendron **2**. (300 MHz,  $\text{CDCl}_3$ )

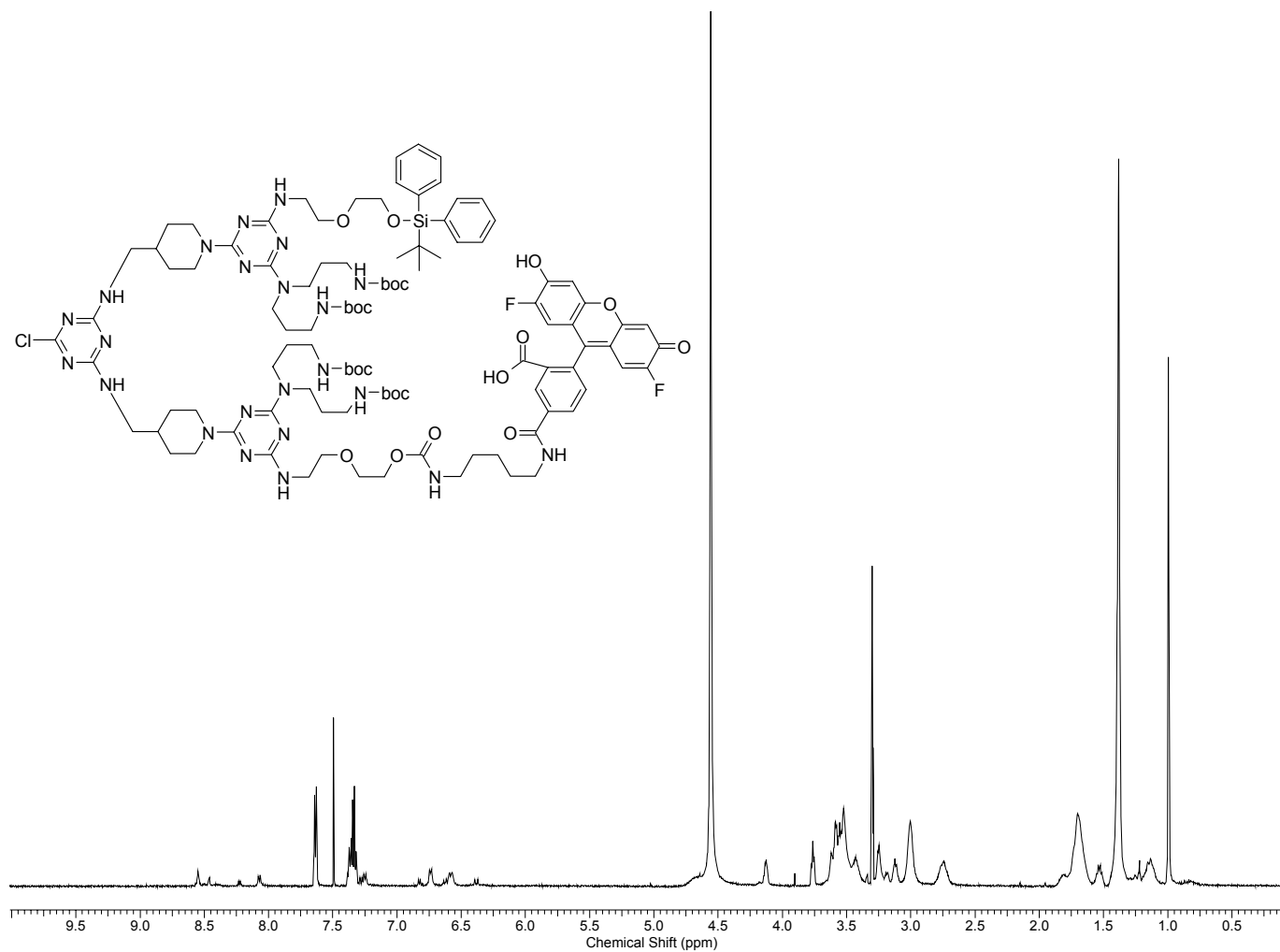


**Figure E.2b.** The  $^{13}\text{C}$  NMR spectrum of dendron 2. (75 MHz,  $\text{CDCl}_3$ )

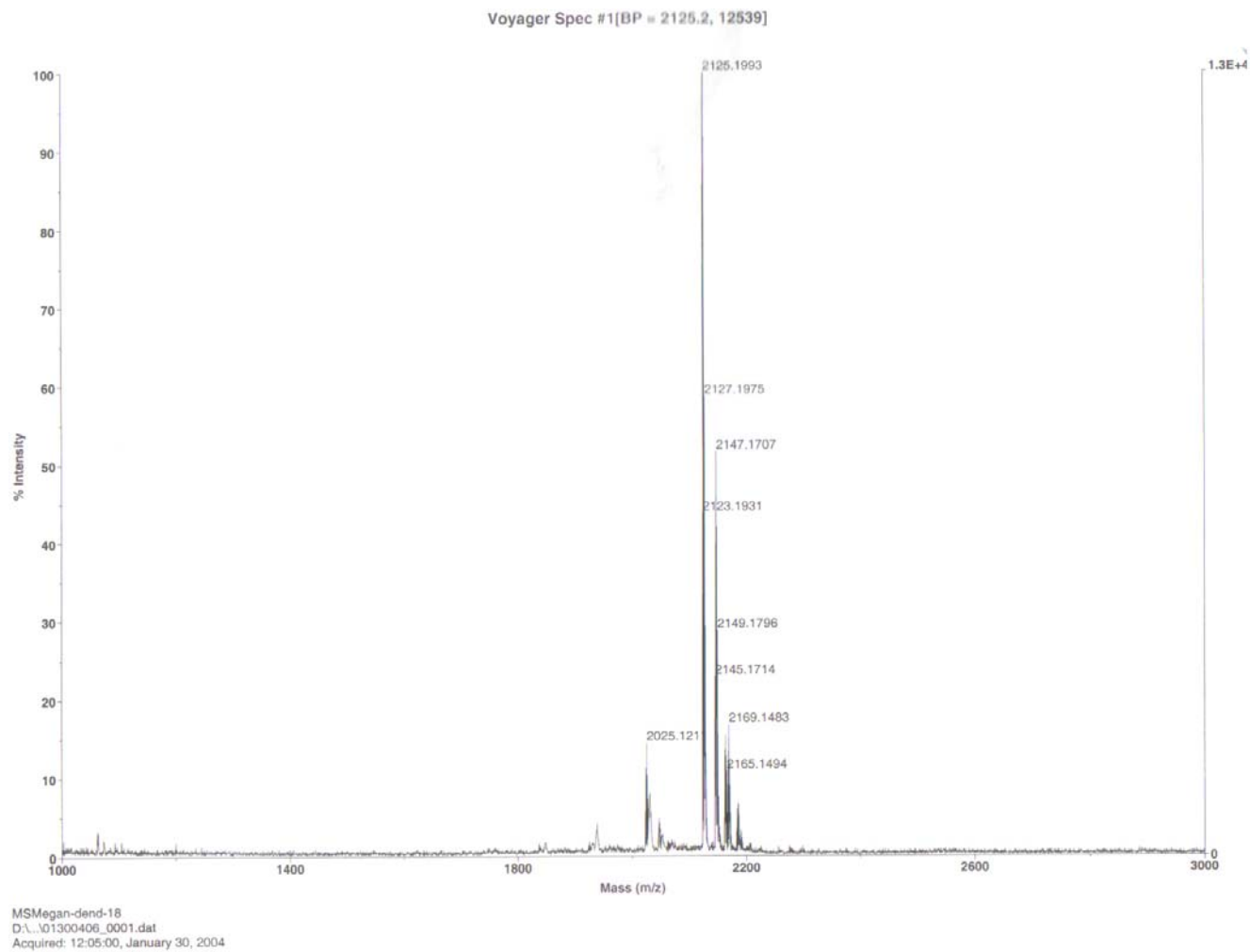


**Figure E.2c.** The MALDI-TOF mass spectrum of dendron **2**.





**Figure E.3a.** The  $^1\text{H}$  NMR spectrum of dendron 3. 500 MHz,  $\text{CDCl}_3$ )



**Figure E.3b.** The MALDI-TOF mass spectrum of dendron 3.

## VITA

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### Publications:

Steffensen, M. B.; Simanek, E. E. Synthesis and Manipulation of Orthogonally Protected Dendrimers: Building Blocks for Library Synthesis. *Angew. Chem. Int. Ed.* **2004**, In Press.

Acosta, E. J.; Steffensen, M. B.; Tichy, S. E.; Simanek, E. E. Removal of Atrazine from Water Using Covalent Sequestration. *J. Agric. Food Chem.* **2004**, 52, 545-549.

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